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(12) # EUROPEAN PATENT SPECIFICATION

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(54) **Dihydropyridine anti-ischaemic and antihypertensive agents, processes for their production, and pharmaceutical compositions containing them.**

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DE-A-2 629 892
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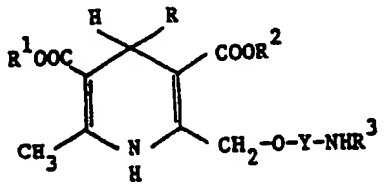
Description

This invention r lates to certan dihydropyridines, specifically to certain 1,4-dihydr pyridines having a basic amino-containing group attached to the 2-position, which have utility as anti-ischaemic and antihypertensive agents.

The compounds of the invention reduce the movement of calcium into the cell and they are thus able to delay or prevent the cardiac contracture which is believed to be caused by an accumulation of intracellular calcium under ischaemic conditions. Excessive calcium influx during ischaemia can have a number of additional adverse effects which would further comprise the ischaemic myocardium. These include less efficient use of oxygen for ATP production, activation of mitochondrial fatty acid oxidation and possibly, promotion of cell necrosis. Thus the compounds are useful in the treatment or prevention of a variety of cardiac conditions, such as angina pectoris, cardiac arrythmias, heart attacks and cardiac hypertrophy. The compounds also have vasodilator activity since they can inhibit calcium influx in cells of vascular tissue and they are thus also useful as antihypertensive agents and for the treatment of coronary vasospasm. Dihydropyridines already known in the art include those of EP—A—0031801, DE—A—2629892, and JP—A—55/47656. The latter application discloses compounds having, in the 2-position, the substituent $—CH_2CH_2NR^6R^7$ where R^6 and R^7 are each lower alkyl or taken together with the N atom to which they are attached represent a heterocycle.

According to the invention, there are provided novel 1,4-dihydropyridine derivatives of the formula:—



(I)

wherein

Y is $—(CH_2)_2—$, $—(CH_2)_3—$, $—CH_2CH(CH_3)—$ or $—CH_2C(CH_3)_2—$;

R is selected from (a) a phenyl group optionally substituted by one or two substituents each selected from nitro, halo, $C_1—C_4$ alkyl, $C_1—C_4$ alkoxy, hydroxy, trifluoromethyl, and cyano, (b) a 1- or 2-naphthyl group, and (c) benzofuranyl; benzothienyl; pyridyl optionally monosubstituted by methyl or cyano; quinolyl; benzoxazolyl; benzothiazolyl; furyl; pyrimidinyl; thiazolyl; 2,1,3-benzoxadiazol-4-yl; 2,1,3-benzothiadiazol-4-yl; or thienyl optionally monosubstituted by halo or $C_1—C_4$ alkyl;

R^1 and R^2 are each independently $C_1—C_4$ alkyl or 2-methoxyethyl; and

R^3 is hydrogen, $C_1—C_4$ alkyl, 2-($C_1—C_4$ alkoxy)ethyl, cyclopropylmethyl, benzyl, or $—(CH_2)_mCOR^4$ where m is 1, 2 or 3 and R^4 is hydroxy, $C_1—C_4$ alkoxy or $—NR^5R^6$ where R^5 and R^6 are each independently hydrogen or $C_1—C_4$ alkyl; and their pharmaceutically acceptable acid addition salts.

The compounds of the formula (I) containing one or more asymmetric centres will exist as one or more pairs of enantiomers, and such pairs or individual isomers may be separable by physical methods, e.g. by fractional crystallisation of the free bases or suitable salts or chromatography of the free bases. The invention includes the separated pairs as well as mixtures thereof, as racemic mixtures or as separated d- and l- optically-active isomeric forms.

The pharmaceutically acceptable acid addition salts of the compounds of the formula (I) are those formed from acids which form non-toxic acid addition salts containing pharmaceutically acceptable anions, such as the hydrochloride, hydrobromide, sulphate, phosphate or acid phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate and gluconate salts. The preferred salts are maleates.

"Halo" means fluoro, chloro, bromo or iodo.

C_3 and C_4 alkyl and alkoxy groups can be straight or branched chain.

R^3 is preferably H, CH_3, benzyl, 2-methoxyethyl, $—CH_2COOCH_3$, $—CH_2COOC_2H_5$, $—CH_2CONHCH_3$, or $—CH_2COOH$.

R^3 is most preferably H or CH_3.

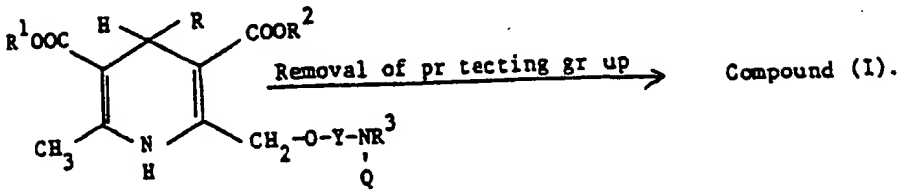
R is preferably 2-chlorophenyl, 2-fluorophenyl, 2-methoxyphenyl, 3-chlorophenyl, 2-chloro-3-hydroxyphenyl, 2-chloro-6-fluorophenyl, unsubstituted phenyl or 2,3-dichlorophenyl.

R^1 is preferably CH_3. R^2 is preferably C_2H_5. Y is preferably $—(CH_2)_2—$ or $—CH_2CH(CH_3)—$. "m" is preferably 1. Most preferably, R is 2-chlorophenyl. Most preferably, Y is $—(CH_2)_2—$.

Th most preferred comp unds have the formula (I) wherein R is 2-chlorophenyl, R^1 is CH_3, R^2 is C_2H_5, R^3 is H or CH_3, and Y is $—(CH_2)_2—$.

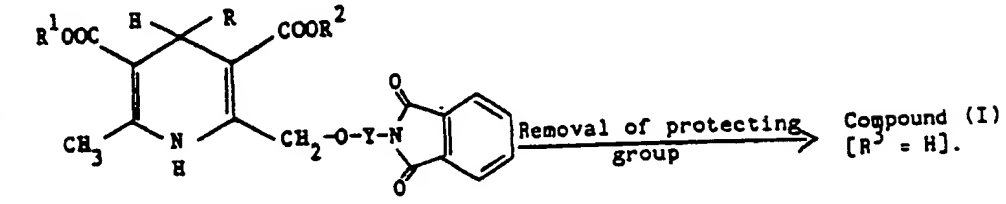
The comp unds of the formula (I) are primary or secondary amines and in one method they can b pr pared by the removal of the amin -pr tecting group from the corresponding amino-protected dihydropyridines.

This general method can be illustrated in more detail as follows:—



(II)

(Q = an amino-protecting group and, R, R^1, R^2, R^3 and Y are as defined for formula [I]);



[R, R^1, R^2 and Y are as defined for formula (I)].

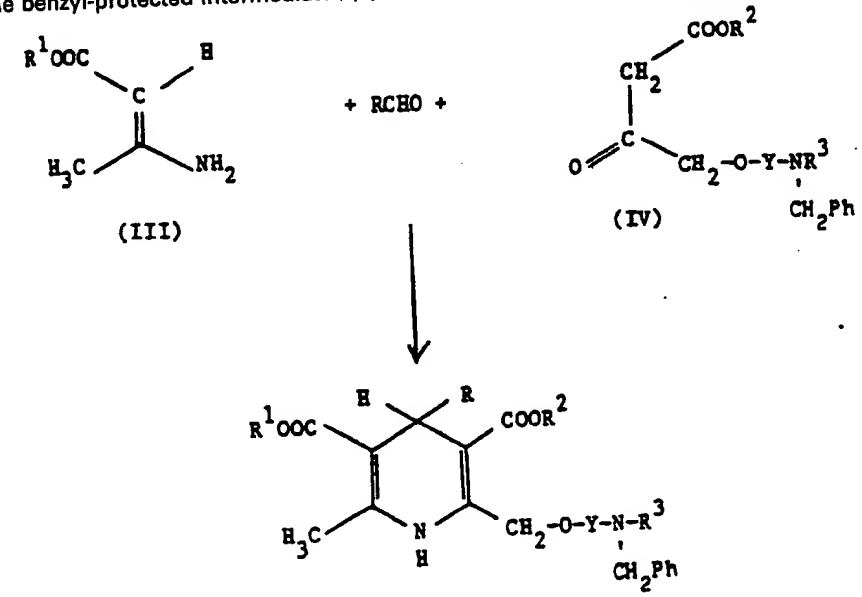
One preferred amino-protecting group is benzyl. It is typically removed by hydrogenation, using e.g. H_2/Pd on charcoal under acidic conditions in a suitable organic solvent, e.g. methanol. The acidic conditions are preferably obtained by using compound (II) in the form of an organic acid addition salt, e.g. as an oxalate or acetic salt.

A typical procedure involving the removal of a benzyl group is as follows. Compound (II) as an oxalate salt in methanol is added to a suspension of 10% pre-hydrogenated palladium on charcoal in methanol, and the mixture is then stirred under hydrogen at 3.44×10^5Pa (50 p.s.i.) for up to about 18 hours, e.g. overnight, and at room temperature. If necessary, heating at up to about 60°C can be provided. The product can then be isolated and purified by conventional procedures.

When both Q and R^3 are benzyl, hydrogenation under the above conditions normally only removes one of the benzyl groups. Further hydrogenation of the resulting monobenzyl product under the above conditions with fresh catalyst can then be used to remove the remaining benzyl group.

Many of the starting materials of the formula (II) in which Q is benzyl are described and claimed in our European patent application publication no. 0060674. Typical methods to the N-benzyl starting materials of the formula (II) are as follows:—

(a) The benzyl-protected intermediates (II) can be prepared by the Hantzsch synthesis, as follows:—



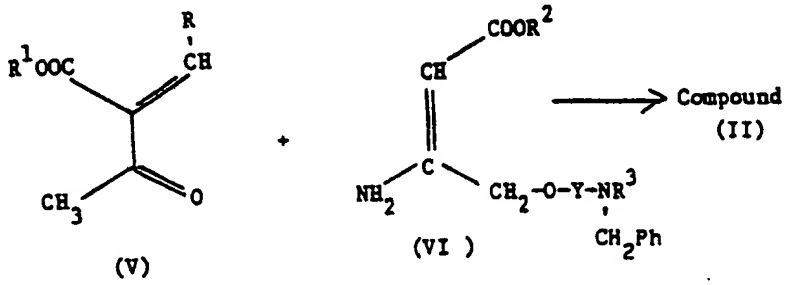
(III) (IV)

In a typical procedure, the ketoester (IV) and aldehyde are heated under reflux in a suitable organic solvent, e.g. a C_1—C_4 alkanol solvent such as ethanol, for about 15 minutes, and then the aminocrotonate

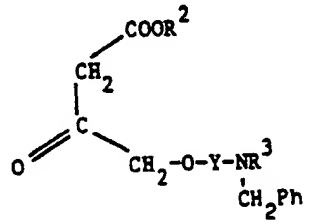
(III) is added. Alternatively the aminocrotonate (III), ketoester (IV) and aldehyde can be heated together in the solvent. Preferably a small amount of a lower alkanoic acid such as acetic acid is added to neutralise the solution. The resulting solution can then be heated at 60°—130°C, preferably under reflux, until the reaction is essentially complete, typically in 24 hours or less. The product of the formula (II) can then be isolated and purified by conventional procedures.

The ketoesters (IV) are either known compounds or can be prepared by methods analogous to those of the prior art, such as the method illustrated in the Preparations hereinafter, which are essentially the method of Troostwijk and Kellogg, J. C. S. Chem. Comm., 1977, page 932. Similarly the amino-crotonates (III) are either known compounds or can be prepared by conventional procedures. Also the aldehydes are either known or can be prepared by known methods.

(b) The benzyl-containing intermediates (II) can also be prepared by the following process:—



The crotonate (VI) is typically prepared *in situ* by reaction of the corresponding acetoacetate (IV):—

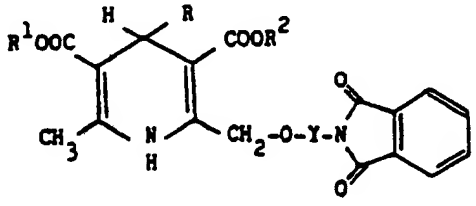


(IV)

with ammonium acetate, e.g. by refluxing in a suitable organic solvent, e.g. a C_1—C_4 alkanol such as ethanol, for, say, up to an hour. The crotonate (VI) is then reacted with compound (V), typically by heating in the solvent for up to about 5 hours at 60°C—130°C, e.g. under reflux. The product (II) can then be isolated and purified by conventional procedures.

The starting materials (V) are either known compounds or may be prepared by methods analogous to those of the prior art, see e.g. Can. J. Chem., 1967, *45*, 1001.

The compounds of the formula (I) in which R^3 is H can be prepared from the corresponding phthalimido derivatives according to conventional procedures, e.g.:



(a) a primary amine
or (b) hydrazine hydrate
or (c) an alkali metal hydroxide
followed by HCl or H_2SO_4.

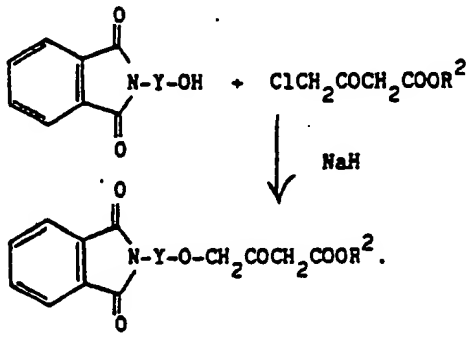
$\sim\sim CH_2OYNH_2$

The preferred amine is methylamine. The preferred alkali metal hydroxide is potassium hydroxide. The reaction using methylamine is typically carried out in ethanol at room temperature, with heating if necessary. The reaction using hydrazine hydrate is typically carried out in ethanol at the reflux temperature or below. The reaction using potassium hydroxide is typically carried out at room temperature (although

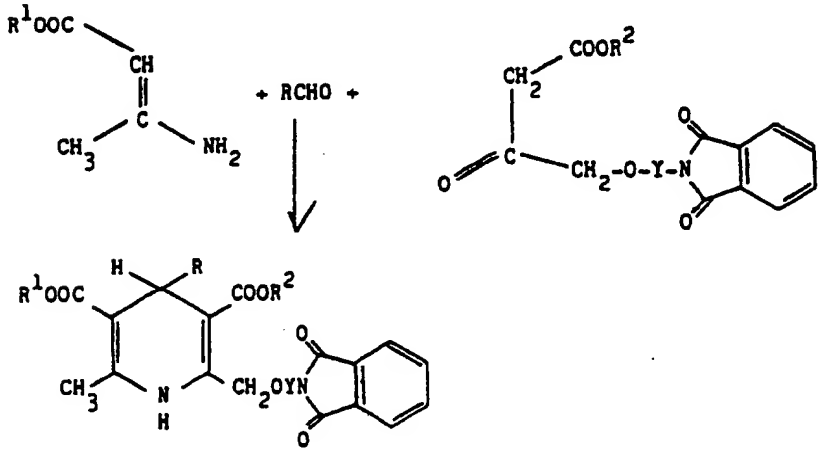
with heating if necessary) in tetrahydrofuran, following by the addition of the acid and heating at the reflux temperature or below. In all cases the product can be isolated conventionally.

The phthalimido starting materials can again be obtained conventionally, e.g.:—

(a)



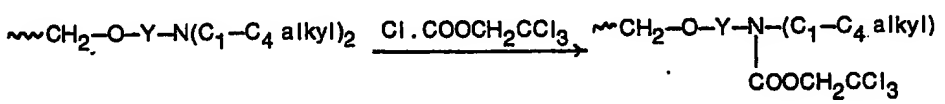
(b)



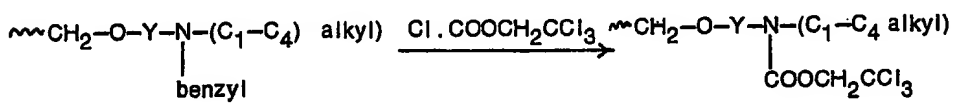
This is again the Hantzsch reaction.

Compounds of the formula (I) in which R^3 is H can also be purified to very high levels by reacting them with phthalic anhydride to form the phthalimido derivatives which can then be converted back to the compounds in which R^3 is H by the methods previously described.

To prepare compounds in which R^3 is C_1—C_4 alkyl, —$COOCH_2CCl_3$ can be used as the amino-protecting group. This can be removed in a conventional manner using zinc and either formic or acetic acid. The N-protected starting materials necessary for this process can be prepared as follows:—

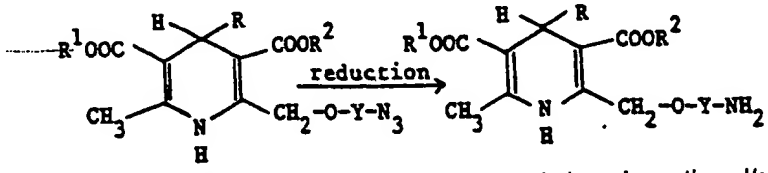


or



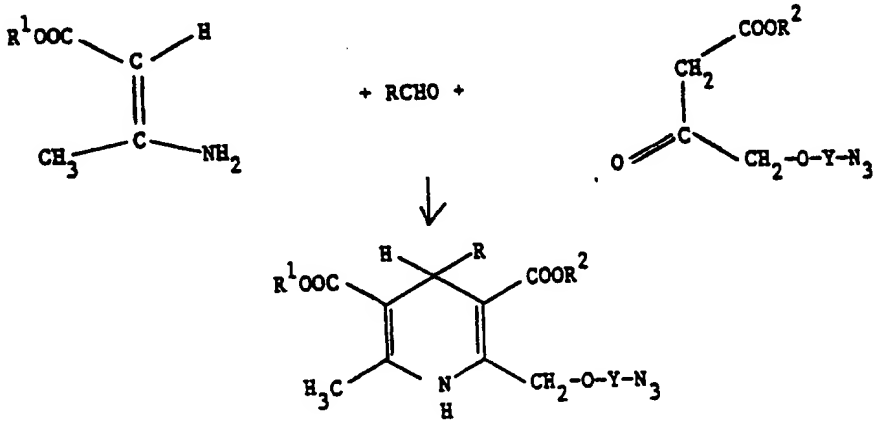
Typically the reaction with 2,2,2-trichloroethyl chloroformate is carried by heating the reactants at up to reflux temperature in e.g. toluene. Many of the dialkylamino and N-alkyl-N-benzylamino starting materials needed to prepared these N-protected intermediates are described and claimed in our corresponding European patent application publication no. 0060674, and others can be prepared analogously.

Th compounds of the formula (I) where R^3 = H can also be obtained from the c rresponding azid comp unds, the azido group being convertabl t —NH_2 by reduction, e.g. with triphenylphosphine, r zinc and hydrochloric acid, or H_2/Pd, under conventi nal conditions.

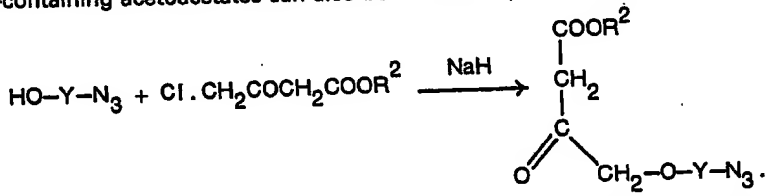


In a typical procedure using zinc dust, the reaction is carried out in methanol/aqueous hydrochloric acid. Heating is possible but is not generally necessary. Similarly hydrogenation can be carried out in e.g. methanol or ethanol in the presence of a catalyst such as Pd/$CaCO_3$ at room temperature.

Again the azido starting materials can be prepared by the Hantzsch synthesis under conditions similar to those previously described:—

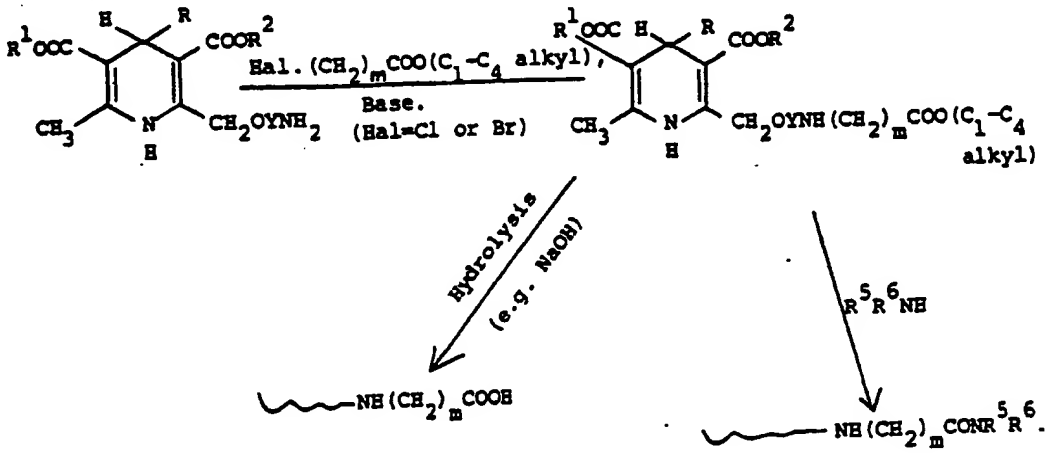


The azido-containing acetoacetates can also be obtained by conventional procedures:—



Similarly the azido starting materials can also be prepared analogously to route (b) above for preparing the N-benzyl starting materials.

Some of the compounds of the invention can be prepared from other compounds of the invention by conventional techniques, e.g.:—



The ability of the compounds to inhibit the movement of calcium into the cell is shown by their effectiveness in reducing the response of isolated heart tissue to an increase in calcium ion concentration *in vitro*. The test is performed by mounting spirally cut strips of rat aorta with one end fixed and the other attached to a force transducer. The tissue is immersed in a bath of physiological saline solution containing potassium ions at a concentration of 45 millimolar and no calcium. Calcium chloride is added to the bath with a pipette to give a final calcium ion concentration of 2 millimolar. The change in tension caused by the resulting contraction of the tissue is noted. The bath is drained and replaced with fresh saline solution and, after 45 minutes, the test is repeated with the particular compound under test present in the saline solution. The concentration of compound required to reduce the response by 50% is recorded.

The antihypertensive activity of the compounds is also evaluated after oral administration by measuring the fall in blood pressure in spontaneously hypertensive rats or renally hypertensive dogs.

For administration to man in the curative or prophylatic treatment of cardiac conditions and hypertension, oral dosages of the compounds will be in the range of from 2—50 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules are likely to contain from 1 to 10 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier. Dosages for intravenous administration would be within the range 1 to 10 mg per single dose as required.

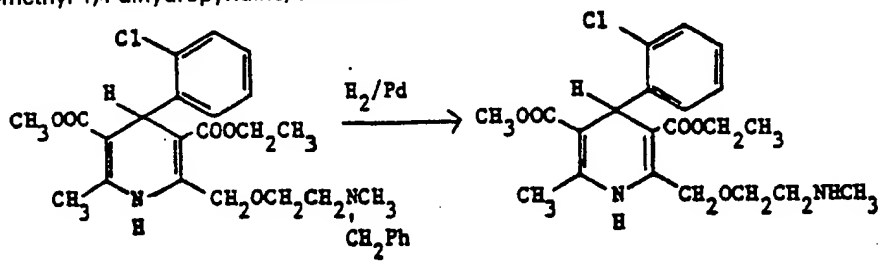
In a further aspect the invention provides a pharmaceutical composition comprising a compound of the formula (I), or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable diluent or carrier.

The invention also provides a compound of the formula (I), or a pharmaceutically acceptable acid addition salt thereof, for use in treating ischaemic heart disease, especially angina, or hypertension, in a human being.

The following Examples illustrate the invention: all temperatures are in °C:—

Example 1

Preparation of 4-(2-chlorophenyl)-2-[2-(methylamino)ethoxymethyl]-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine, oxalate salt



A solution of 2 - [2 - (N - benzyl - N - methylamino)ethoxymethyl] - 4 - [2 - chlorophenyl] - 3 - ethoxycarbonyl - 5 - methoxycarbonyl - 6 - methyl - 1,4 - dihydropyridine, oxalate salt (4.3 g) in methanol (220 ml) was added to a suspension of 10% (by weight) palladium on charcoal (0.4 g) prehydrogenated in methanol (50% ml). Stirring under hydrogen at 3.44 × 10^5Pa (50 p.s.i.) and room temperature overnight resulted in complete removal of the benzyl group. After removal of the catalyst by filtration, the methanol was removed by evaporation and the residue crystallised from a little methanol to give the title compound (2.4 g), m.p. 211°.

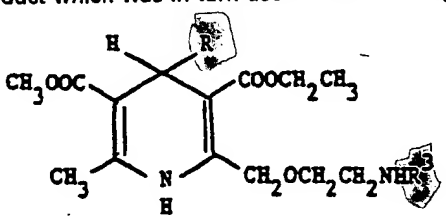
Analysis%:—

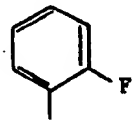
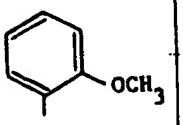
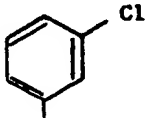
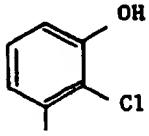
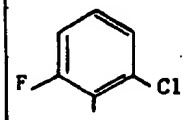
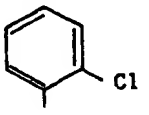
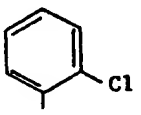
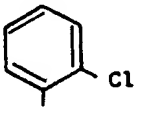
Calculated for $C_{21}H_{27}ClN_2O_5.C_2H_2O_4$:	C, 53.85;	H, 5.70;	N, 5.46;
Found:	C, 53.99;	H, 5.76;	N, 5.60.

The free base had a m.p. of 88—90° (from ether).

Examples 2—10

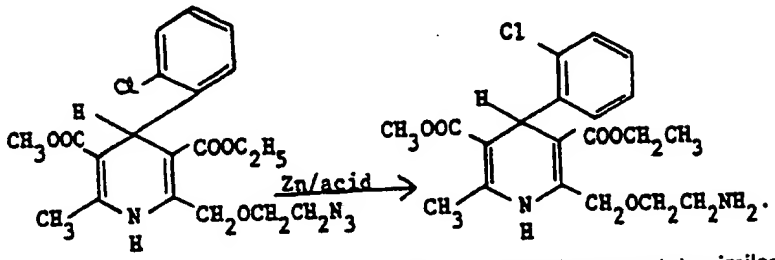
The following compounds were prepared similarly to the method described in Example 1 and were characterised in the form indicated, starting from the appropriate N-substituted dihydropyridine oxalate and H_2/Pd. It should be noted that hydrogenation of the N,N-dibenzyl starting material in Example 8 produced the monobenzyl product which was in turn used as the starting material in Example 9.



Example No.	R	R^3	Form Characterised	m.p. (°C)	Analysis % (Theoretical in brackets) C	H	N
2	—Ph	$-CH_3$	free base	79—80	65.14 (64.93	7.33 7.26	7.09 7.21)
3		$-CH_3$	oxalate	205—7	55.35 (55.64	5.84 5.84	5.60 5.64)
4		$-CH_3$	free base	103—5	63.87 (63.14	7.60 7.23	6.56 6.70)
5		$-CH_3$	oxalate	204—5	54.14 (53.85	5.71 5.70	5.57 5.46)
6		$-CH_3$	oxalate	203—4	52.14 (52.22	5.68 5.49	5.29 5.30)
7		$-CH_3$	oxalate	197—9	52.03 (52.03	5.41 5.30	5.06 5.30)
8		$-CH_2Ph$	oxalate	185	59.18 (59.13	5.75 5.65	4.86 4.76)
9		—H	maleate	169	54.83 (54.91	5.55 5.57	5.34 5.34)
10		$-CH_2CH_2OCH_3$	oxalate	105—7	53.57 (53.91	6.10 5.97	4.91 5.03)

Example 11

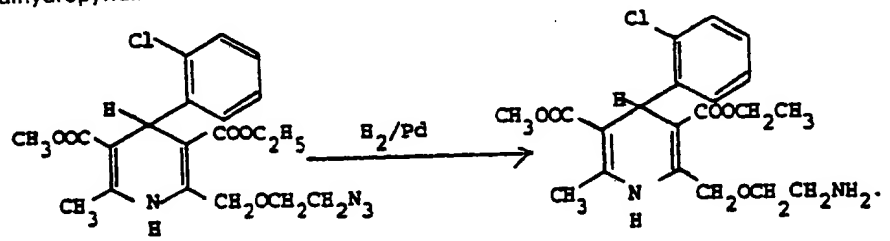
Preparation of 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine maleate



2-Azidoethanol (3 g) was converted to ethyl 4-(2-azidoethoxy)acetoacetate similarly to the method described in Preparation 3 hereinafter using ethyl 4-chloroacetoacetate, and the crude ketoester (not characterised) was used in the Hantzsch reaction using the method described in Preparation 9, i.e. by reacting it with methyl 3-aminocrotonate and 2-chlorobenzaldehyde. The crude Hantzsch product (not characterised) dissolved in methanol (250ml) and 3N hydrochloric acid (200 ml) was stirred on a water bath at room temperature while zinc dust (15 g) was added portionwise over 10 minutes. After stirring a further 10 minutes the solution was decanted from excess zinc, the methanol evaporated and the aqueous acid residue washed with toluene (100 ml), basified with concentrated ammonia and extracted with methylene chloride (2 × 100 ml). The extracts were dried (Na_2CO_3), filtered and evaporated to dryness. The residue in toluene was chromatographed on a medium pressure column of silica (T.L.C. grade, Merck "Kieselgel" [Trade Mark] 60H, 7 g) eluting initially with toluene, changing gradually to methylene chloride and then to methylene chloride plus 3% methanol. Appropriate fractions were combined and converted to the maleate salt in ethyl acetate. Recrystallisation from acetone and ethyl acetate (1:1) gave the title compound (maleate salt) (190 mg, 1% yield from 2-azido ethanol) as a white solid, m.p. 169°, identical by t.l.c. with the product obtained in Example 9.

Example 12

Preparation of 2-[2-aminoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine maleate



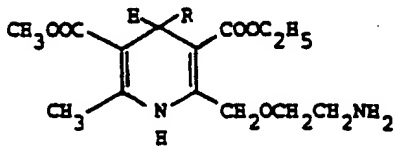
A suspension of 2-(2-azidoethoxy)methyl-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (103 g) in ethanol (2.5 l) was stirred for 16 hours at room temperature under an atmosphere of hydrogen in the presence of 5% palladium on calcium carbonate (40 g). The reaction mixture was filtered and evaporated and the residue treated with a solution of maleic acid (22 g) in ethanol (100 ml). The reaction mixture was stirred at room temperature for two hours and then the resulting solid collected, washed with ethanol, and dried to give the title compound (100 g), m.p. 169—170.5°.

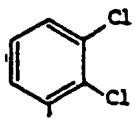
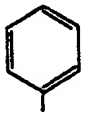
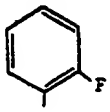
Analysis%:—

Found:	C, 54.82;	H, 5.62;	N, 5.46
$C_{20}H_{25}ClN_2O_5.C_4H_4O_4$ requires:	C, 54.91;	H, 5.57;	N, 5.34.

Examples 13—15

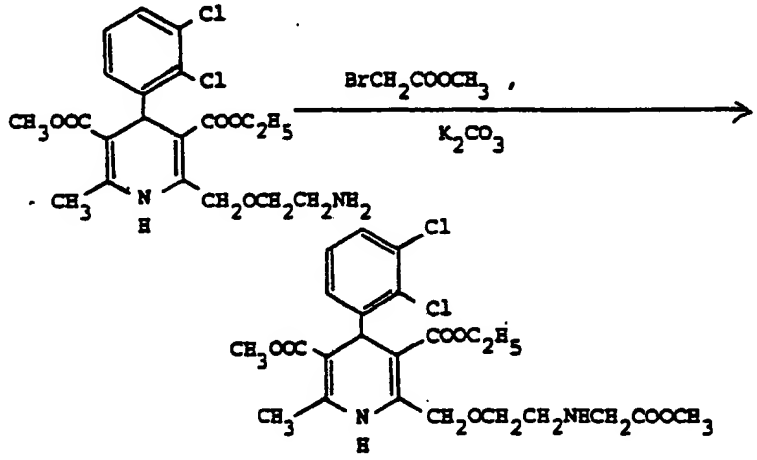
Th following compounds were prepared similarly to Example 12 from the approprite azide and H_2/Pd:—



Example No.	R	Form characterised	m.p. (°C)	Analysis % (Theoretical in brackets) C	H	N
13		½ fumarate ½ hydrate	171—173	51.7 (51.8	5.3 5.3	5.5 5.5)
14		fumarate ½ hydrate	158—168	57.6 (57.7	6.2 6.3	5.8 5.6)
15		fumarate	152	56.95 (56.68	6.02 5.75	5.93 5.5)

Example 16

Methyl N-(2-{[4-(2,3-dichlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyrid-2-yl]methoxy}ethyl)aminoacetate



A solution of methyl bromoacetate (1.53 g) in acetonitrile (20 ml) was added dropwise over 30 minutes to a stirred, refluxing mixture of 2-[(2-aminoethoxy)methyl]-4-(2,3-dichlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (5.01 g) and potassium carbonate (2.76 g) in acetonitrile (60 ml). The mixture was then heated under reflux for 3 hours, filtered, and evaporated. The residue was partitioned between ethyl acetate and water and the organic layer washed with water, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica (t.l.c. grade Merck Kieselgel 60H, [Trade Mark] 40g) eluting with dichlor methane plus 0—3% methanol. Appropriate fractions wer combined and evaporated to give th title c pound (2.10 g), m.p. 96—98°.

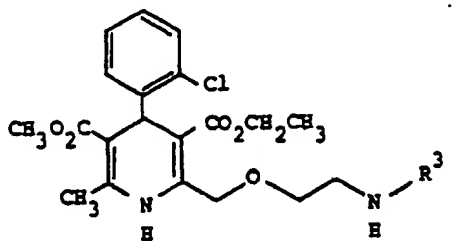
Analysis %:—

Found: C, 53.25; H, 5.49; N, 5.48;

$C_{23}H_{28}Cl_2N_2O_7$ requires: C, 53.60; H, 5.48; N, 5.44.

Examples 17 and 18

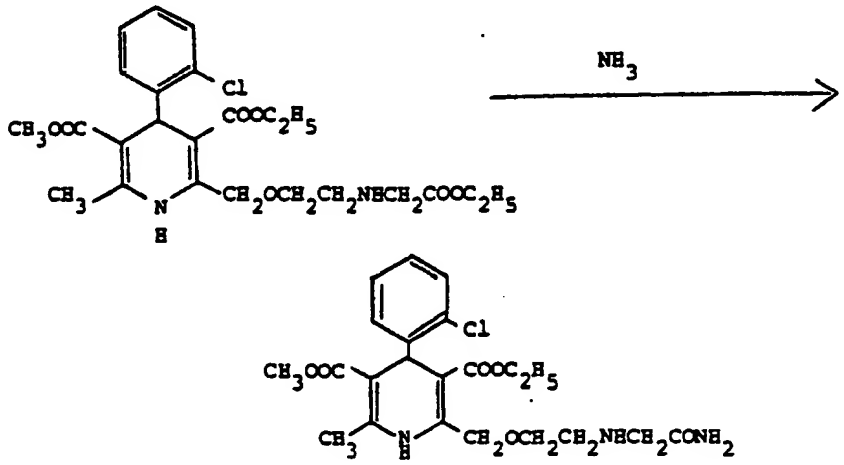
The following compounds were prepared by the method described in Example 16 using appropriate starting materials.



Example No.	R^3	m.p. (°C)	Analysis % or n.m.r. (Theoretical in brackets) C	H	N
17	$-CH_2CO_2CH_2CH_2$	78—80	58.26 (58.24	6.30 6.31	5.65 5.66)
18	$-CH_2CO_2CH_3$	oil	*n.m.r.* ($CDCl_3$). τ values: 7.72 (1H, broad s); 6.96—7.51 (4H, m); 5.43 (1H, s); 4.78 (2H, s); 4.10 (2H, q); 3.78 (3H, s); 3.63 (3H, s); 3.3—3.7 (6H, m); 2.38 (3H, s); 1.20)3H, t);		

Example 19

2-(2-{[4-(2-Chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyrid-2-yl]-methoxy}ethylamino)acetamide



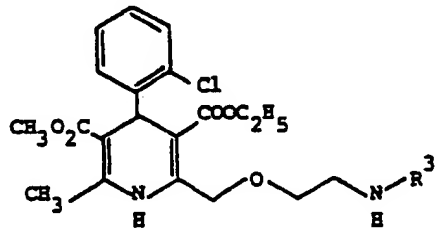
Ethyl N - (2 - {[4 - (2 - chlorophenyl) - 3 - ethoxycarbonyl - 5 - methoxycarbonyl - 6 - methyl - 1,4 - dihydropyrid - 2 - yl]methoxy}ethyl)aminoacetate (2.50 g) in a mixture of ethanol (40 ml) and 0.880 aqueous ammonia (30 ml) was stirred at room temperature for four days and then evaporated. The residue was partitioned between ethyl acetate and water and the organic layer washed with water, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica (t.l.c. grade Merck Kieselgel 60H, [Trade Mark] 30 g) eluting with dichloromethane plus 0—5% methanol. Appropriate fractions were combined and

vap rated. Th residue was triturated with ethyl acetate and th resulting solid collected, washed with ethyl acetate, and dried to giv the titl c mpound (1.23 g), m.p. 126—129°.

Analysis %:—
Found: C, 56.78; H, 6.06; N, 8.68;
$C_{22}H_{28}ClN_3O_6$ requires: C, 56.71; H, 6.06; N, 9.02.

Example 20

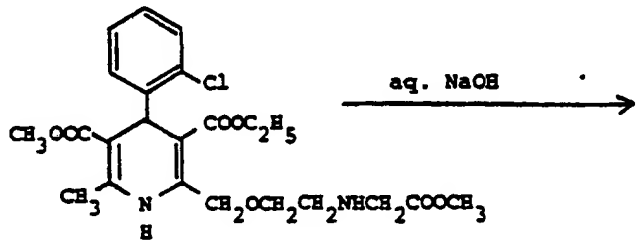
The following compound was prepared by the method described in Example 19 using the same dihydropyridine and methylamine.

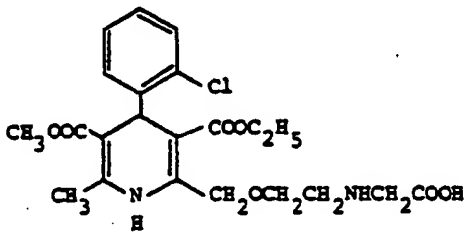


Example No.	R^3	m.p. (°C)	Analysis % or n.m.r. (Theoretical in brackets) C	H	N
20	$-CH_2CONHCH_3$	123—124	57.80 (57.56	6.55 6.30	8.73 8.76)

Example 21

N-(2-{[4-(2-Chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyrid-2-yl]-methoxy}ethyl)aminoacetic acid hemihydrate



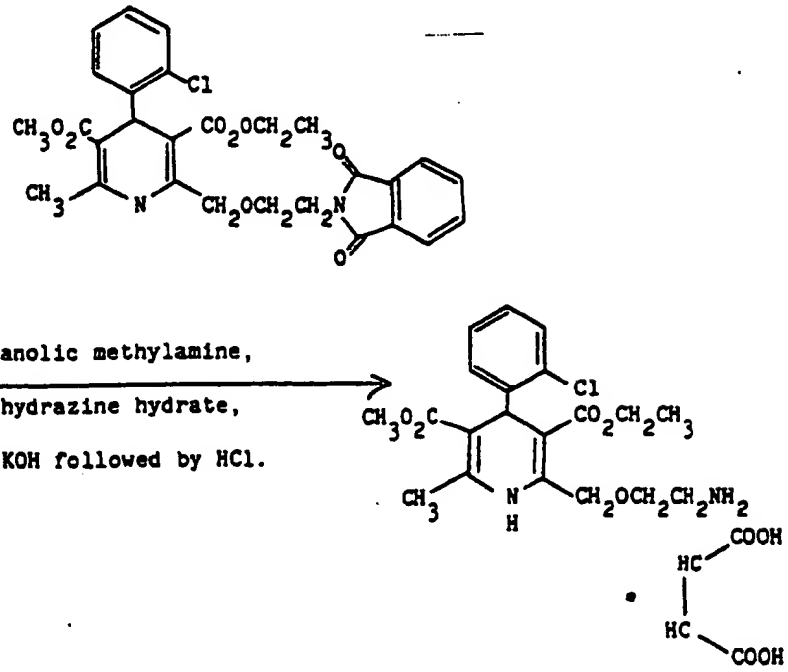


A solution of methyl N - (2 - {[4 - (2 - chlorophenyl) - 3 - ethoxycarbonyl - 5 - methoxycarbonyl - 6 - methyl - 1,4 - dihydropyrid - 2 - yl]methoxy}ethyl)aminoacetate (2.40 g) in dioxane (80 ml) was treated with 1M aqueous sodium hydroxide solution (10 ml) and the mixture stirred at room temperature for 2 hours and then evaporated. The residue was purified by ion exchange chromatography (Bio-Rad AG 50W—X8, [Trade Mark], 200—400 mesh, cation form, 40 g) eluting with dioxane initially followed by 2% pyridine in water. Appropriate fractions were combined and evaporated to give the title compound as a hemihydrate (0.56 g), m.p. 140—150°C (decomp.).

Analysis %:—
Found: C, 55.52; H, 5.95; N, 5.92;
$C_{22}H_{27}ClN_2O_7.\frac{1}{2}H_2O$ requires: C, 55.52; H, 5.93; N, 5.89.

Example 22

Preparati n f 2-[(2-amin eth xy)m thyl]-4-(2-chlorophenyl)-3-eth xycarbonyl-5-methoxycarb nyl-6-methyl-1,4-dihydropyridine mal at



Method A (using ethanolic methylamine

4 - (2 - Chlorophenyl) - 3 - ethoxycarbonyl - 5 - methoxycarbonyl - 6 - methyl - 2 - (2 - phthalimidoethoxy)methyl - 1,4 - dihydropyridine (80 g) was stirred in 33% ethanolic methylamine solution (1067 ml) at room temperature for three hours. The solvent was then evaporated and the residue was slurried in industrial methylated spirits (300 ml) then filtered. To the filtrate was added maleic acid (17.4 g) and after stirring a precipitate was produced. This was collected by filtration and was washed with industrial methylated spirits. The solid was crystallised from industrial spirits (430 ml) and dried at 55° to give the title compound (38.4 g) as a white solid confirmed spectroscopically to be identical with the products of Examples 9 and 12.

Method B (using hydrazine hydrate)

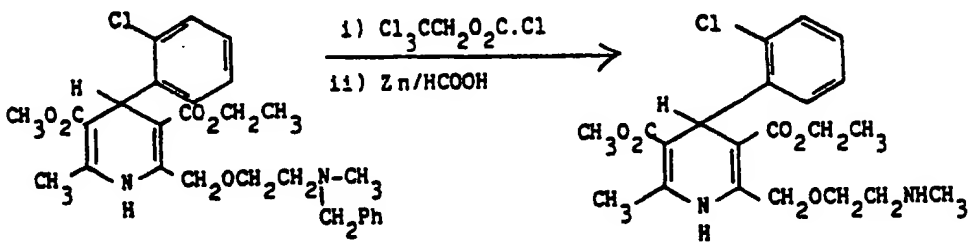
4 - (2 - Chlorophenyl) - 3 - ethoxycarbonyl - 5 - methoxycarbonyl - 6 - methyl - 2 - (2 - phthalimidoethoxy)methyl - 1,4 - dihydropyridine (383 g) was stirred in refluxing ethanol containing hydrazine hydrate (106.7 g). After two hours, the reaction mixture was cooled and filtered. The filtrate was evaporated and the residue was dissolved in methylene chloride (2000 ml) and the solution was washed with water (2000 ml). The organic solution was evaporated and the residual oil was dissolved in industrial methylated spirit (1120 ml). To this solution was added maleic acid (82.5 g) and the resulting precipitate was collected, washed with industrial methylated spirit and dried at 55° to give the title compound (304 g) as a white solid, again confirmed spectroscopically to be the desired product.

Method C (using KOH followed by HCl).

4 - (2 - Chlorophenyl) - 3 - ethoxycarbonyl - 5 - methoxycarbonyl - 6 - methyl - 2 - (2 - phthalimidoethoxy)methyl - 1,4 - dihydropyridine (15 g) was dissolved in a mixture of tetrahydrofuran (150 ml) and water (100 ml) containing potassium hydroxide (3.13 g). After stirring at room temperature for 1.5 hours 2N hydrochloric acid (100 ml) was added and the resulting slurry was refluxed for 2.5 hours. The solution was extracted twice with methylene chloride (2 × 100 ml) and the combined extracts were dried ($MgSO_4$) and evaporated to leave an oil which was diss lved in industrial methylated spirits (57 ml). Maleic acid (3.24 g) was added and th resulting precipitate was collected, washed with industrial methylated spirits and dried at 55° to give the title compound (10.2 g) as an off-white solid, again c nfirmed spectroscopically to be the desired product.

Example 23

Preparation of 4-(2-Chlorophenyl)-2-[2-(N-methylamino)ethoxymethyl]-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine maleate



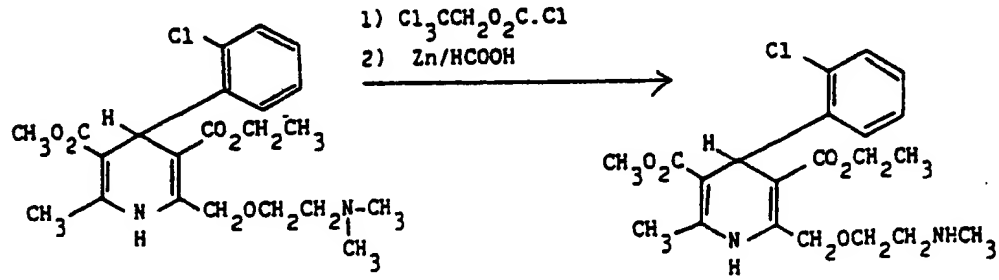
A mixture of 2 - [2 - (N - benzyl - N - methylamino)ethoxymethyl] - 4 - [2 - chlorophenyl] - 3 - ethoxycarbonyl - 5 - methoxycarbonyl - 6 - methyl - 1,4 - dihydropyridine (4.8 g) and 2,2,2-trichloroethyl chloroformate (2.7 g) was heated in toluene at reflux for 20 hours. After cooling to room temperature, the mixture was stirred with 1N hydrochloric acid (50 ml) and extracted with ether. The extracts were evaporated to leave a crude oil (6.9 g) containing the corresponding 2-[2-(N-2,2,2-trichloroethoxycarbonyl-N-methylamino)ethoxymethyl] derivatives.

The said oil (3.0 g) was dissolved in dimethylformamide (10.5 ml) and formic acid (0.5 g) and at 5° zinc (0.7 g) was added.

The mixture was allowed to warm to room temperature and kept for three days at this temperature. The reaction mixture was then decanted and poured into water (100 ml) and acidified to pH1 with concentrated hydrochloric acid. The aqueous solution was washed with *n*-hexane (50 ml) then 0.88 ammonia solution was added to give a precipitate. This was collected and dried before dissolving in ethyl acetate. Maleic acid (0.34 g) was added followed by ether. After trituration, the solid was collected and dried to give a solid confirmed by NMR and IR to be (apart from the salt form) identical to the product of Example 1.

Example 24

Preparation of 4-(2-chlorophenyl)-2-[2-(N-methylamino)ethoxymethyl]-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine maleate

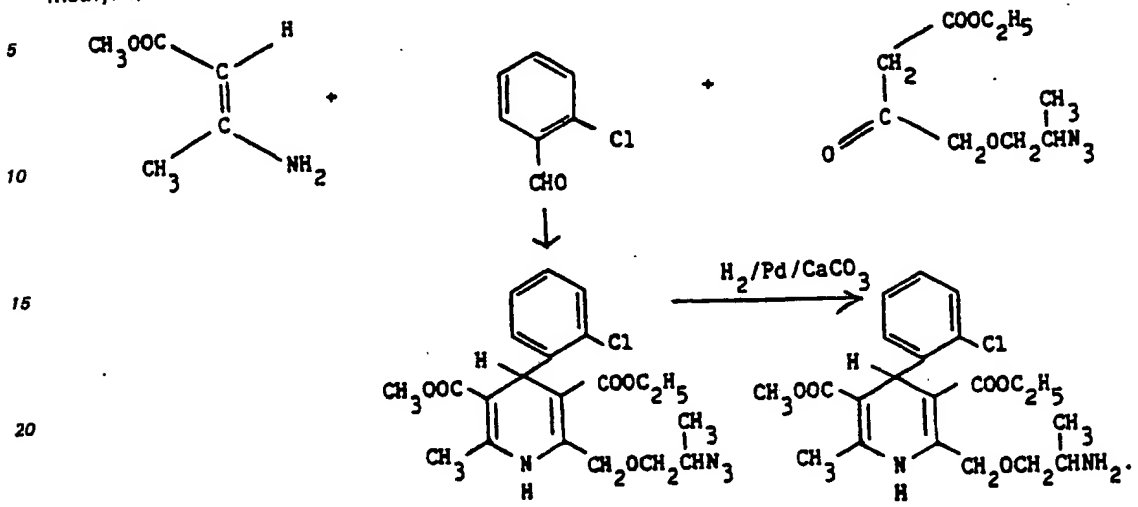


4 - [2 - Chlorophenyl] - 2 - [2 - (N,N-dimethylamino)ethoxymethyl] - 3 - ethoxycarbonyl - 5 - methoxycarbonyl - 6 - methyl - 1,4 - dihydropyridine (147.6 g) and 2,2,2-trichloroethylchloroformate (98.7 g) were stirred together in refluxing toluene for 20 hours. The reaction mixture was then cooled t room temperature and 1N hydrochloric acid (1147 ml) was added. The mixture was extracted twice with ether (2 × 1147 ml) and the extracts were bulked and evaporated to leave a crude oil (201.6) containing the corresponding 2 - [2 - (N - 2,2,2 - trichloroethoxycarbonyl - N - methylamino)ethoxymethyl] derivative.

This oil (196 g) was dissolved in dimethylformamide (686 ml) and formic acid (35.5 g) and the mixture was cooled to 5°. Zinc (50.5 g) was added in portions over 20 minutes and then the mixture was stirred at r om temp rature f r 90 hours. The reaction mixture was decanted, added to water (1500 ml), and then taken to pH1 with concentrated hydrochl ric acid. The aqueous soluti n was washed with *n*-h xane (500 ml) and the remaining aqueous phase was adjust d to pH10 with 0.88 amm nia soluti n. The resulting mixture was granulated and the s lid was coll ct d and dried t giv th crude pr duct (138 g). This solid was dissolved in hot ethyl acetate containing maleic acid (37.1 g) and on c ling the title c mp und was obtained (82.3 g) as a white solid confirm d sp ctroscopically to be id ntical to the product of Example 23.

Example 25

Preparation of 2-(2-aminoprop-1-oxymethyl)-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine hemifumarate hemihydrate



A mixture of ethyl 2-(2-azidoprop-1-oxy)acetoacetate (13.05 g), 2-chlorobenzaldehyde (8.3 g) and methyl 3-aminocrotonate (6.8 g) in methanol (80 ml) was heated under reflux for 19 hours, reduced to half-volume, and then cooled overnight at −20°. The resulting precipitate was collected, washed with a little cold methanol, and dried to give 2 - (2 - azidoprop - 1 - oxymethyl) - 3 - ethoxycarbonyl - 5 - methoxycarbonyl - 6 - methyl - 1,4 - dihydropyridine (4.0 g) as a pale yellow solid, m.p. 115°, characterised spectroscopically.

A suspension of the above product (4.0 g) in methanol (100 ml) was stirred under one atmosphere of hydrogen at room temperature in the presence of palladium on calcium carbonate (1.0 g) for 18 hours. The mixture was then filtered through "Solkafloc" (Trademark) and evaporated. The residue was dissolved in methanol (20 ml), treated with a warm solution of fumaric acid (1.00 g) in methanol (10 ml), and stored overnight at 0°. The resulting solid was collected, recrystallised from ethanol, and dried to give the title hemifumarate hemihydrate (2.4 g), m.p. 180—183°.

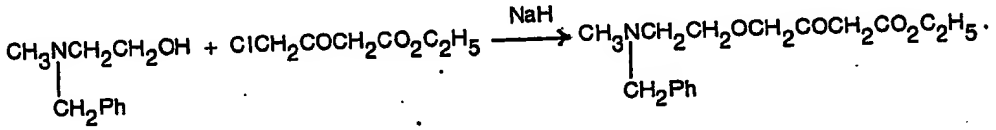
Analysis %:—

Found:	C, 56.46;	H, 6.63;	N, 5.68;
Calculated for $C_{21}H_{27}ClN_2O_5.\frac{1}{2}C_4H_4O_4.\frac{1}{2}H_2O$:	C, 56.38;	H, 6.17;	N, 5.72.

The following Preparations illustrate the preparation of certain starting materials. All temperatures are in °C:—

Preparation 1

Preparations of Ethyl 4-[2-(N-benzyl-N-methylamino)ethoxy]acetoacetate



Sodium hydride (60% (by weight) in oil, 8 g) was stirred in dry tetrahydrofuran (THF) (100 ml) under nitrogen while 2-(N-benzyl-N-methylamino)ethanol (17 g) was added slowly. The warm mixture was stirred for 1 hour, then kept cool on a water bath at room temperature (20°) while a solution of ethyl 4-chloroacetoacetate (16.5 g) in dry THF (100 ml) was added dropwise over 3.5 hours. The mixture was stirred overnight at room temperature under nitrogen, then quenched with a little ethanol and poured onto ice (100 g) and concentrated hydrochloric acid (30 ml). The THF was removed by evaporation, and the residue washed with light petroleum (b.p. 60—80°) to remove mineral oil. The residue was basified with solid sodium carbonate and extracted with ethyl acetate (200 ml and 100 ml). The combined extracts were dried (Na_2CO_3), filtered and evaporated to give the title compound as an oil (30 g), sufficiently pure for further use.

N.m.r. spectrum in $CDCl_3$, δ values: 7.27 (5H, s); 4.12 (2H, q); 4.06 (2H, s); 3.45—3.70 (6H, m); 2.61 (2H, t); 2.25 (3H, s); 1.23 (3H, t).

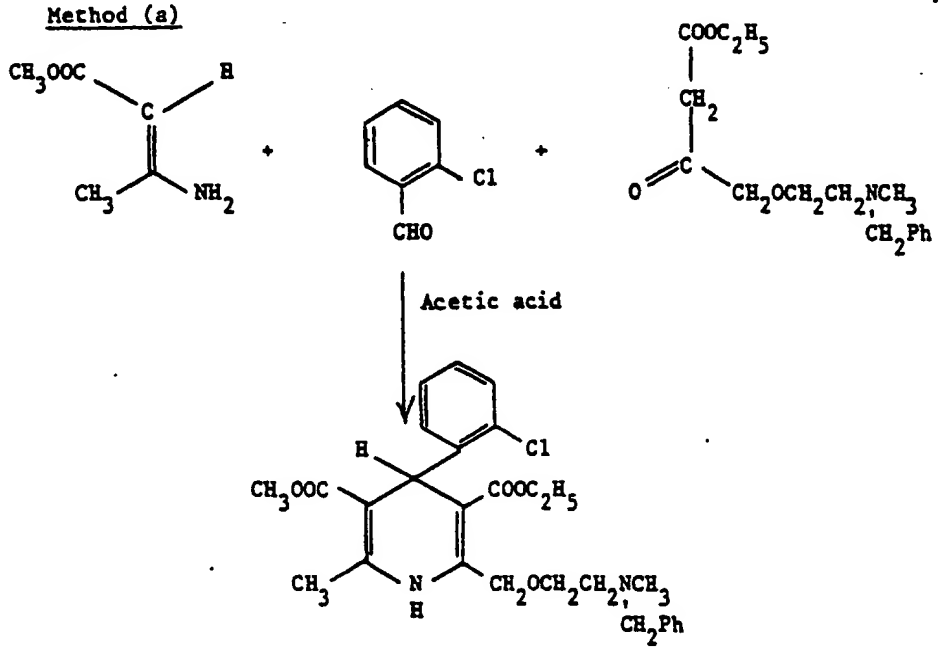
The following acetoacetates were prepared similarly to the above, starting from the appropriate N-substituted 2-aminoethanol and ethyl 4-chloroacetoacetate, and were used directly without characterisation:—

$R^3NCH_2CH_2OCH_2COCH_2CO_2C_2H_5$ where R^3 = —CH_2Ph or —$CH_2CH_2OCH_3$.
|
CH_2Ph

Preparation 2

Preparation of 2-[2-(N-benzyl-N-methylamino)ethoxymethyl]-4-(2-chloro-phenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine, oxalate salt

Method (a)

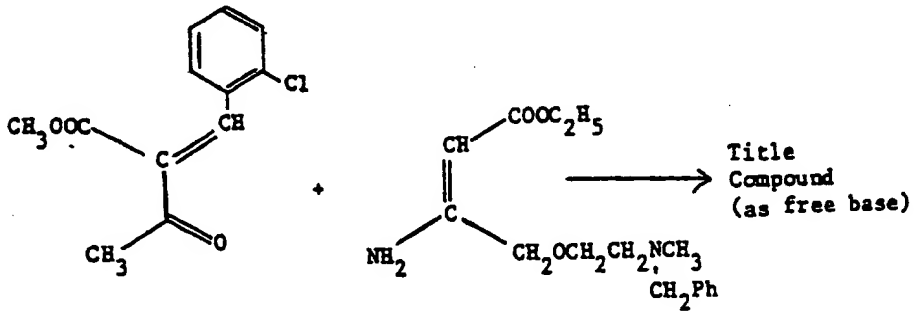


Ethyl 4-[2-(N-benzyl-N-methylamino)ethoxy]acetoacetate (25 g), 2-chlorobenzaldehyde (11 g), methyl 3-aminocrotonate (9.1 g) and acetic acid (5 ml) in ethanol (100 ml) were mixed and heated under reflux for 3.5 hours. The cooled reaction mixture was then evaporated to dryness and the residue partitioned between 2N hydrochloric acid (200 ml) and methylene chloride (300 ml). The methylene chloride solution was washed with saturated sodium carbonate solution (200 ml), dried ($MgSO_4$), filtered and evaporated to dryness. The residue in ether was treated with an excess of oxalic acid dissolved in ether to precipitate the crude product. The precipitate was recrystallised from methanol to give the title compound (6.5 g) as a white solid, m.p. 181°.

Analysis:—

Calculated for $C_{28}H_{33}ClN_2O_5.C_2H_2O_4$:	C, 59.75;	H, 5.85;	N, 4.65
Found:	C, 59.42;	H, 5.85;	N, 4.39.

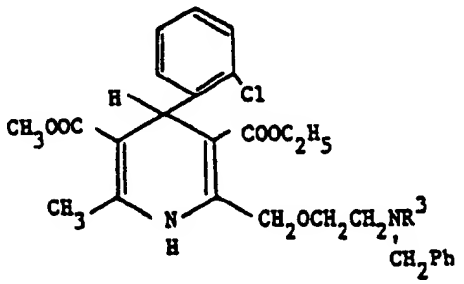
Method (b)



Ethyl 4-[2-(N-benzyl-N-methylamino)ethoxy]acetoacetat (141 g) and ammonium acetate (37.3 g) in ethanol (280 ml) were heated gently und r reflux for 20 minutes. The methyl 2-(2-chlorobenzylidine)

acetoacetate (115 g) was added and h ating under reflux continued for 4 hours. The cooled reaction mixture was vaporated to dryness, re-dissolved in toluene (200 ml), and extracted with 2N hydrochloric acid (2 × 150 ml). The thick oily layer in the aqueous phase, and th aqueous phas itself, were extracted with methylene chloride (400 ml and 200 ml), and the combined extracts were washed with excess saturated sodium carb nate s lution and dried (Na_2CO_3). The methylene chl ride was rem ved by evaporation and the residue in toluene plus 20% petrol was filtered through a medium pressure column of silica (T.L.C. grade, Merck "Kieselgel" [Trade Mark] 60H, 100 g) eluting with toluene plus 20% petrol (500 ml) and then toluene (1 litre). The combined eluates were evaporated to dryness to give the crude title compound as the free base, an oil (177 g), sufficiently pure by t.l.c. for use in the subsequent hydrogenation step.

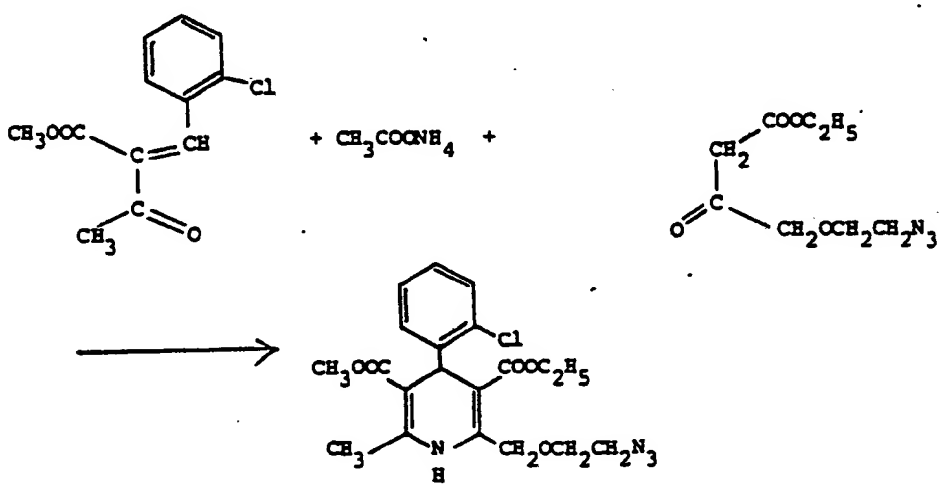
The following starting materials were also prepared similarly to (b) above, starting from the appropriate N-substituted acetoacetates and ammonium acetate, and were used directly without characterisation:—



where R^3 = $-CH_2Ph$ or $-CH_2CH_2OCH_3$.

Preparation 3

2-(2-Azidoethoxy)methyl-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine



A solution of 2-azidoethanol (160 g) in tetrahydrofuran (300 ml) was added over 40 minutes to a suspension of sodium hydride (114 g; 80% dispersion in oil) in tetrahydrofuran (500 ml). The mixture was stirred at room temperature for 1 hour, then cooled in ice water and treated dropwise with a solution of ethyl 4-chloroacetoacetate (276 g) in tetrahydrofuran (250 ml) over 2 hours. The mixture was stirred at room temperature for 16 hours, diluted with ethanol (150 ml), and the pH adjusted to 6—7 with 4M hydrochloric acid. Sufficient water was added to dissolve the solid present and the layers were separated. The organic layer was evaporated and the residue diluted with water (600 ml) and evaporated. The residue was partitioned between ethyl acetate and water and the aqueous layer extracted twice with ethyl acetate. The combined ethyl acetate extracts were dried ($MgSO_4$) and evaporated to give ethyl 4-(2-azidoethoxy)-acetoacetate as a brown oil, which was shown by g.l.c. to be 73% pure. A mixtur of this crude product and amm nium acetate (92.3 g) in ethan l (600 ml) was heated under reflux for 1 hour, allowed to co l to room temperature, and treated with m thyl 2-(2-chlorobenzylidene)acetoacetate (286.6 g). The mixture was heated under reflux for 5.5 hours and then evaporated. The residue was stirred with methanol (1.5 l) for 16

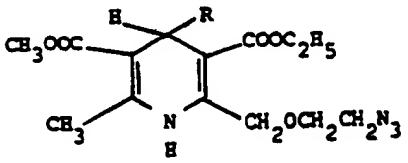
h urs and the resulting solid collected, washed twice with m thanol, dried, and recrystallised from methan l t give the title c mp und (78 g), m.p. 145—146°.

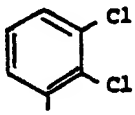
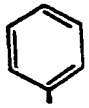
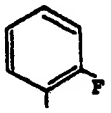
Analysis %:—

Found:	C, 55.39;	H, 5.37;	N, 13.01
Calculated for $C_{20}H_{23}ClN_4O_5$:	C, 55.23;	H, 5.33;	N, 12.88.

Preparations 4 to 6

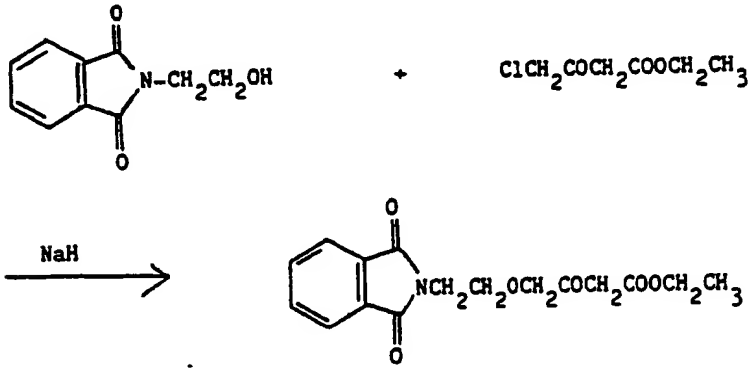
The following azides were prepared similarly to Preparation 3 from appropriate starting materials:—



Preparation No.	R	m.p. (°C)	Analysis % (Theoretical in brackets) C	H	N
4		141	50.88 (51.18	4.78 4.73	11.73 11.94)
5		124	59.64 (59.99	6.11 6.04	13.98 13.99)
6		129—130	*n.m.r.* in $CDCl_3$: δ = 7.14 (5H, m); 5.28 (1H, s); 4.80 (2H, s); 4.04 (2H, q); 3.65 (4H, m); 3.62 (3H, s); 2.35 (3H, s); 1.20 (3H, t).		

Preparation 7

Preparation of ethyl 4-[2-(phthalimido)ethoxy]acetoacetate



Sodium hydride (57% [by weight] in oil, 66.1 g) was stirred in dry tetrahydrofuran (500 ml) under nitrogen at −10° while N-(2-hydroxyethyl)phthalimide (150 g) was added. To this slurry was added at −10° a soluti n of ethyl 4-chlor acetoacetate (129.3 g), in dry tetrahydrofuran, ver 1 hour. Th reaction mixture was then allowed t warm to room temperature and stirring was continu d for 18 hours. This mixture was pour d into 1N hydrochloric acid (800 ml) and ethyl acetat was add d (750 ml). Th aqueous layer was washed with ethyl acetate (300 ml) and the rganic soluti ns w re combined. After washing with water

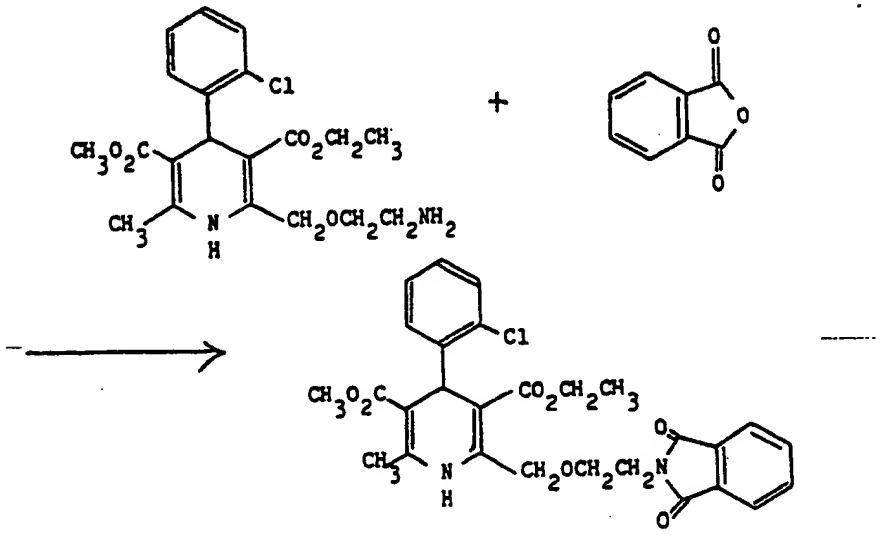
(300 ml), th ethyl acetate was evaporated to giv th title comp und as a crude oil (243 g), sufficiently pure f r further us .

. *N.m.r. spectrum* in $CDCl_3$, δ values: 7.80 (4H, m); 4.15 (2H, s); 4.10 (2H, q); 3.92 (2H, t); 3.78 (2H, t); 3.49 (2H, s); 1.22 (3H, t).

Preparation 8

Preparation of 4-(2-Chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-2-(2-phthalimido-ethoxy)methyl-1,4-dihydropyridine ———

(A.) From 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine

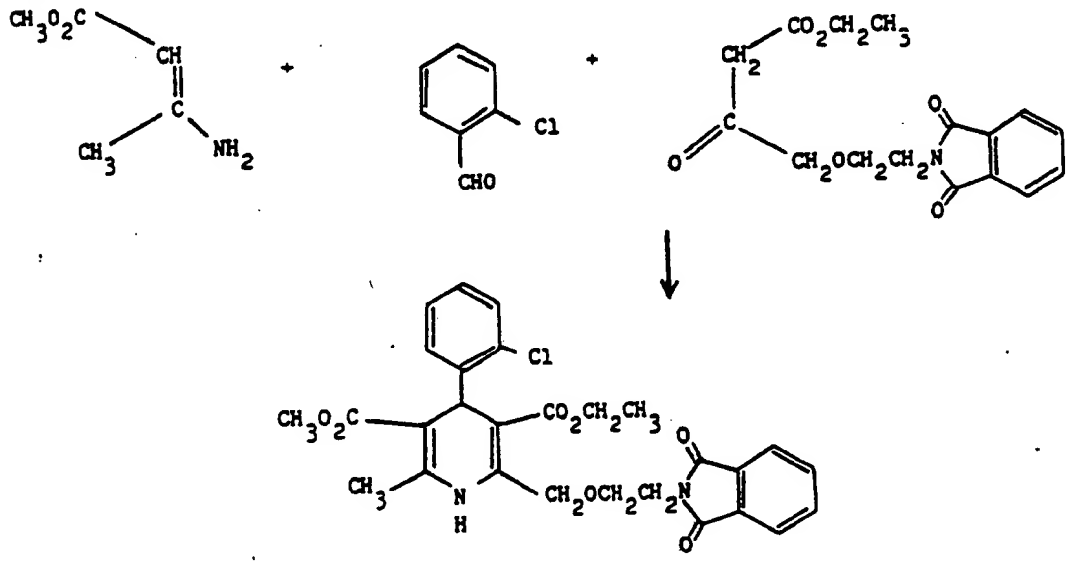


2 - [2 - Aminoethoxy)methyl] - 4 - (2 - chlorophenyl) - 3 - ethoxycarbonyl - 5 - methoxycarbonyl - 6 - methyl - 1,4 - dihydropyridine (2.0 g) and phthalic anhydride (0.73 g) were stirred in refluxing acetic acid (20 ml) for 2.5 hours. After cooling, the insoluble material was collected and stirred in methanol (10 ml). Filtration gave the title compound (1.0 g) as a white solid, m.p. 146—147°.

Analysis %:—

Found:	C, 62.18;	H, 5.02;	N, 5.20
Calculated for $C_{28}H_{27}ClN_2O_7$:	C, 62.39;	H, 5.05;	N, 5.20.

(B.) From ethyl 4-[2-(phthalimido)ethoxy]acetoacetate

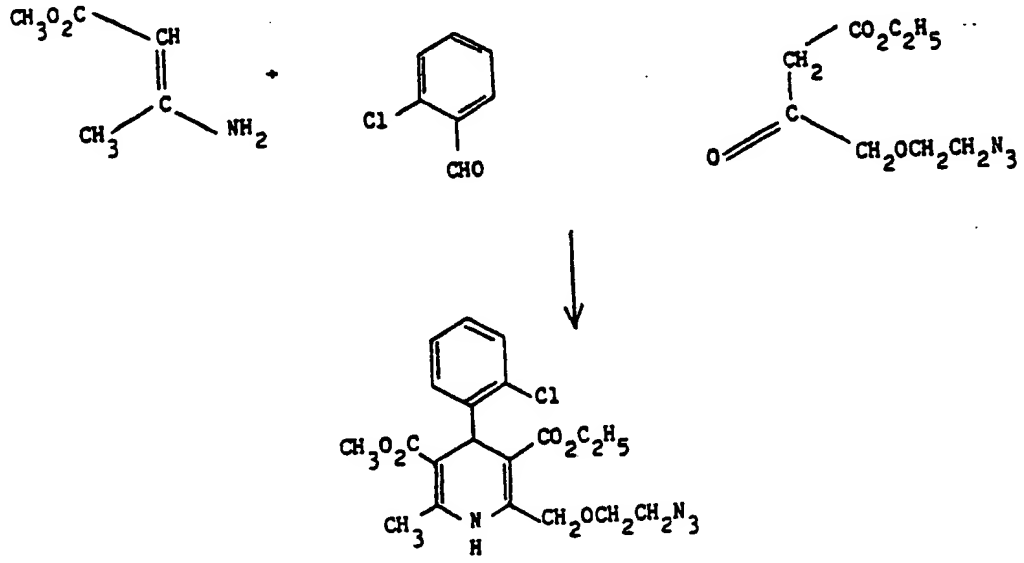


Ethyl 4-(2-(phthalimid)ethoxy]acetoacetate (200 g) was dissolved in isopropanol (1000 ml) and to this was added 2-chlor benzaldehyd (88.1 g) and methyl 3-aminocrotonate (72.2 g). The mixture was refluxed

for 21 hours then the methanol was evap rated to leave an oil which was dissolved in acetic acid (1000 ml). After granulating overnight, the precipitate was collected, washed with acetic acid then slurried in m thanol (300 ml). Filtration gave th title compound the n.m.r. and ir of which were identical with th s of the material prepared by part (A) abov .

Preparation 9

Preparation of 2-(2-Azidoethoxy)methyl-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine



Ethyl 4-(2-azidoethoxy)acetoacetate (46.4 g), prepared from 2-azidoethanol similarly to the method described in Preparation 3, was reacted with methyl 3-aminocrotonate (24.8 g) and 2-chlorobenzaldehyde (30.3 g) in methanol (150 ml) at reflux for 18 hours. After cooling to room temperature, the resulting solid was collected, washed twice with methanol and dried to give the title compound (28 g). The product could be crystallised from methanol, acetone or ethyl acetate. It was used directly.

Preparation 10

Preparation of ethyl 4-(2-azidoprop-1-oxy)acetoacetate

(a) $CH_3CH(Br)CH_2OH + NaN_3 \longrightarrow CH_3CH(N_3)CH_2OH$

(b) $CH_3CH(N_3)CH_2OH + ClCH_2COCH_2COOC_2H_5 \xrightarrow[ii)\ HCl]{i)\ NaH} CH_3CH(N_3)CH_2OCH_2COCH_2COOC_2H_5$

A mixture of 2-bromopropan-1-ol (J. Am. Chem. Soc., 7681, *96*, [1974]) (19.75 g) and sodium azide (10.0 g) was heated on a steam-bath for four days, allowed to cool to room temperature, and then washed four times with ether. The combined ether washings were filtered and evaporated to give 2-azidopropan-1-ol (12.3 g) as a pale brown oil which was shown by g.l.c. to be 98% pure.

A solution of 2-azidopropan-1-ol (10.1 g) in tetrahydrofuran (100 ml) was added over two minutes to a stirred, ice-cooled suspension of sodium hydride (6.6 g; 80% dispersion in oil) in tetrahydrofuran (50 ml). The mixture was stirred for 15 minutes with ice-cooling and then treated over 20 minutes with a solution of ethyl 4-chloroacetoacetate (16.4 g) in tetrahydrofuran (150 ml). The mixture was stirred at room temperature for 16 hours and evaporated. The residue was diluted with water, washed twice with ether, acidifi d with 2M hydr chloric acid, and extracted three times into ether. The combined ether extracts w re dried (Na_2SO_4) and evaporated to giv crude ethyl 4-(2-azidoprop-1-oxy)acetoac tate (20 g), used directly.

Activity Data

The molar concentration of the c mpounds rquired to reduce the response by 50% in the test specified on pages 14—15 is given b low (IC_{50} values) (1M = 1 gm.mole/litre). Th smaller th c ncentration th

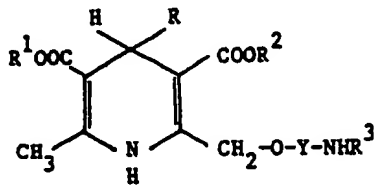
more activ th c mpound, i.e., th most active c mpounds are the products of Examples 1, 9, 11, 12, 22, 23 and 24.

IC_{50} Valu s

Compound	IC_{50}
Product of Example 1	3.2×10^{-9} M
Product of Example 2	3.2×10^{-8} M
Product of Example 3	2×10^{-8} M
Product of Example 4	6.3×10^{-8} M
Product of Example 5	4×10^{-8} M
Product of Example 6	2×10^{-7} M
Product of Example 7	1.3×10^{-8} M
Product of Example 8	5×10^{-8} M
Product of Example 9	3.2×10^{-9} M
Product of Example 10	2.5×10^{-8} M
Product of Example 11	3.2×10^{-9} M
Product of Example 12	3.2×10^{-9} M
Product of Example 13	6.3×10^{-9} M
Product of Example 14	1.6×10^{-7} M
Product of Example 15	1.8×10^{-8} M
Product of Example 19	4×10^{-9} M
Product of Example 20	2.2×10^{-8} M
Product of Example 22	3.2×10^{-9} M
Product of Example 23	3.2×10^{-9} M
Product of Example 24	3.2×10^{-9} M

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A dihydropyridine of the formula:—



(I)

or a pharmaceutically acceptable acid addition salt thereof wherein

Y is $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2CH(CH_3)-$ or $-CH_2C(CH_3)_2-$;

R is select d from (a) a phenyl group optionally substituted by on or two substituents each s l cted fr m nitro, halo, C_1—C_4 alkyl, C_1—C_4 alk xy, hydroxy, triflu romethyl, and cyano, (b) a 1- r 2-naphthyl group, and (c) benzofuranyl; benz thienyl; pyridyl opti nally mon substituted by methyl r cyan ;

quinolyl; benzoxazolyl; benzothiazolyl; furyl; pyrimidinyl; thiazolyl; 2,1,3-benzoxadiazol-4-yl; 2,1,3-benzothiadiazol-4-yl; or thienyl optionally monosubstituted by halo or C_1—C_4 alkyl;

R^1 and R^2 are each independently C_1—C_4 alkyl or 2-methoxyethyl; and

R^3 is hydrogen, C_1—C_4 alkyl, 2-(C_1—C_4 alkoxy)ethyl, cyclopropylmethyl, benzyl, or —$(CH_2)_mCOR^4$ where m is 1, 2 or 3 and R^4 is hydroxy, C_1—C_4 alkoxy or —NR^5R^6 where R^5 and R^6 are each independently hydrogen or C_1—C_4 alkyl.

2. A compound as claimed in claim 1, wherein R is phenyl, 2-chlorophenyl, 2-fluorophenyl, 2-methoxyphenyl, 3-chlorophenyl, 2-chloro-3-hydroxyphenyl, 2-chloro-6-fluorophenyl, or 2,3-dichlorophenyl.

3. A compound as claimed in either of the preceding claims, wherein Y is —$(CH_2)_2$ or —$CH_2CH(CH_3)$—.

4. A compound as claimed in any one of the preceding claims, wherein R^3 is H, CH_3, benzyl, 2-methoxyethyl, —CH_2COOCH_3, —$CH_2COOC_2H_5$, —CH_2CONH_2, —$CH_2CONHCH_3$ or —CH_2COOH.

5. A compound as claimed in claim 4, wherein R^3 is H or CH_3.

6. A compound as claimed in claim 1, wherein R is 2-chlorophenyl, R^1 is CH_3, R^2 is C_2H_5, Y is —$(CH_2)_2$— and R^3 is H or CH_3.

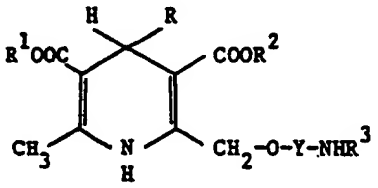
7. A compound as claimed in any one of the preceding claims, which is in the form of a maleate salt.

8. A pharmaceutical composition comprising a compound of the formula (I) or a pharmaceutically acceptable acid addition salt thereof together with a pharmaceutically acceptable diluent or carrier.

9. A compound of the formula (I) or a pharmaceutically acceptable acid addition salt thereof as claimed in any one of claims 1 to 7, for use in treating ischaemic heart disease, especially angina, or hypertension, in a human being.

Claims for the Contracting State: AT

1. A process for the preparation of a 1,4-dihydropyridine of the formula:—



(I)

or a pharmaceutically acceptable acid addition salt thereof

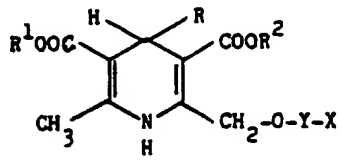
wherein

Y is —$(CH_2)_2$—, —$(CH_2)_3$—, —$CH_2CH(CH_3)$— or —$CH_2C(CH_3)_2$—;

R is selected from (a) a phenyl group optionally substituted by one or two substituents each selected from nitro, halo, C_1—C_4 alkyl, C_1—C_4 alkoxy, hydroxy, trifluoromethyl, and cyano, (b) a 1- or 2-naphthyl group, and (c) benzofuranyl; benzothienyl; pyridyl optionally monosubstituted by methyl or cyano; quinolyl; benzoxazolyl; benzothiazolyl; furyl; pyrimidinyl; thiazolyl; 2,1,3-benzoxadiazol-4-yl; 2,1,3-benzothiadiazol-4-yl; or thienyl optionally monosubstituted by halo or C_1—C_4 alkyl;

R^1 and R^2 are each independently C_1—C_4 alkyl or 2-methoxyethyl; and

R^3 is hydrogen, C_1—C_4 alkyl, 2-(C_1—C_4 alkoxy)ethyl, cyclopropylmethyl, benzyl, or —$(CH_2)_mCOR^4$ where m is 1, 2 or 3 and R^4 is hydroxy, C_1—C_4 alkoxy or —NR^5R^6 where R^5 and R^6 are each independently hydrogen or C_1—C_4 alkyl, characterised by the removal of the amino-protecting group from an amino-protected 1,4-dihydropyridine of the formula:—



(IA)

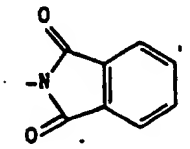
wherein R, R^1, R^2 and Y are as defined above, and X is, as appropriate, a protected primary or secondary amino group, said secondary amino group having the formula —NHR^3 where R^3 is as defined for formula (I) except for hydrogen, said process being followed by, optionally, one or more of the following steps:—

(a) conversion of a compound of the formula (I) in which R^3 is H into a compound of the formula (I) in which R^3 is —$(CH_2)_mCOO(C_1$—C_4 alkyl) where m is 1, 2 or 3 by reaction with a compound of the formula Hal-$(CH_2)_m$ $COO(C_1$—C_4 alkyl) where "Hal" is Cl or Br;

(b) conversion of a compound of the formula (I) in which R^3 is —$(CH_2)_m$ $COO(C_1$—C_4 alkyl) where m is 1, 2 or 3 into a compound of the formula (I) in which R^3 is —$(CH_2)_m$ COOH or —$(CH_2)_mCONR^5R^6$, m, R^5 and R^6 being as defined for formula (I), by, respectively, hydrolysis or reaction with an amine of the formula R^5R^6NH; and

(c) conversion of a compound of the formula (I) into a pharmaceutically acceptable acid addition salt by reaction with a non-toxic acid.

2. A process according to claim 1, wherein X is —NR^3 (benzyl) where R^3 is as defined for formula (I), —$NR^3(COOCH_2CCl_3)$ where R^3 is C_1—C_4 alkyl, or a group of the formula:—

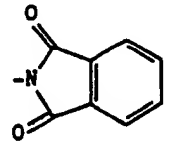


3. A process according to claim 2, wherein X is NR^3(benzyl), said benzyl group being removed by treating compound (IA) with hydrogen.

4. A process according to claim 3, which is carried out in the presence of a palladium catalyst under acidic conditions.

5. A process according to claim 2, wherein X is —$NR^3(COOCH_2CCl_3)$ and said —$COOCH_2CCl_3$ group is removed by treatment of the compound (IA) with zinc in formic or acetic acid.

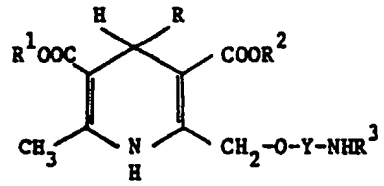
6. A process according to claim 1, wherein X is a group of the formula:



the phthaloyl group being removed by treating compound (IA) with ether (a) a primary amine (b) hydrazine hydrate or (c) an alkali metal hydroxide and then with hydrochloric or sulphuric acid.

7. A process according to claim 6, wherein said primary amine is methylamine, and said alkali metal hydroxide is potassium hydroxide.

8. A process for the preparation of a 1,4-dihydropyridine of the formula:—



(I)

or a pharmaceutically acceptable acid addition salt thereof,

wherein

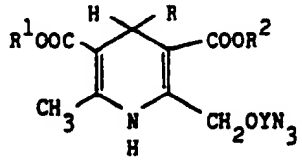
Y is —$(CH_2)_2$—, —$(CH_2)_3$, —$CH_2CH(CH_3)$— or —$CH_2C(CH_3)_2$—;

R is as defined in claim 1;

R^1 and R^2 are each independently C_1—C_4 alkyl or 2-methoxyethyl; and

R^3 is H or —$(CH_2)_mCOR^4$ where m is 1, 2 or 3, and

R^4 is hydroxy, C_1—C_4 alkoxy or —NR^5R^6 where R^5 and R^6 are each independently hydrogen or C_1—C_4 alkyl, characterised by reducing an azido compound of the formula:—



where R, R^1, R^2 and Y are as defined for formula (I) so as to produce a compound of the formula (I) in which R^3 is H, said process being followed by, optionally, one or more of the following steps:—

(a) conversion of a compound of the formula (I) in which R^3 is H into a compound of the formula (I) in which R^3 is —$(CH_2)_mCOO(C_1$—C_4 alkyl) where m is 1, 2 or 3 by reaction with a compound of the formula Hal-$(CH_2)_m$ $COO(C_1$—C_4 alkyl) where "Hal" is Cl or Br;

(b) conversion of a compound of the formula (I) in which R^3 is —$(CH_2)_m$ $COO(C_1$—C_4 alkyl) where m is 1, 2 or 3 into a compound of the formula (I) in which R^3 is —$(CH_2)_m$ COOH or —$(CH_2)_mCONR^5R^6$, m, R^5 and R^6 being as defined for formula (I), by, respectively, hydrolysis or reaction with an amine of the formula R^5R^6NH; and

(c) conversion of a compound of the formula (I) into a pharmaceutically acceptable acid addition salt by reaction with a non-toxic acid.

9. A process according to claim 8, wherein the reduction is carried out with hydrogen.

10. A process acc rding to claim 9, wherein the hydr genati n is carried ut in the presence of a palladium catalyst.

11. A process acc rding to claim 8, wherein the reduction is carried out with zinc and hydr chloric acid.

12. A process according to any one of claims 1 to 7, characterised in that it is used to prepare compounds of the formula (I) in which R is 2-chlorophenyl, R^1 is CH_3, R^2 is C_2H_5, Y is $—(CH_2)_2$ and R^3 is H or CH_3.

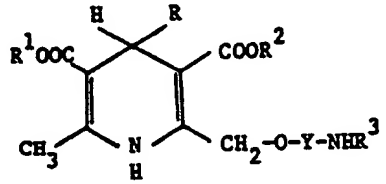
13. A process according to any one of claims 8 to 11, characterised in that it is used to prepare compounds of the formula (I) in which R is 2-chlorophenyl, R^1 is CH_3, R^2 is C_2H_5, Y is $—(CH_2)_2—$ and R^3 is H.

14. A process for preparing a pharmaceutical composition which comprises preparing a compound of the formula (I) as defined in claim 1 or a pharmaceutically acceptable acid addition salt thereof by a process as claimed in any one of the preceding claims, followed by mixing the thus-produced product with a pharmaceutically acceptable diluent or carrier.

15. A process for preparing a pharmaceutical composition, which comprises mixing a compound of the formula (I) as defined in claim 1 or a pharmaceutically acceptable acid addition salt thereof, with a pharmaceutically acceptable diluent or carrier.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Dihydropyridin der Formel:



(I)

oder ein pharmaze tisch verwendbares Säureadditionssalz davon worin

Y $—(CH_2)_2—$, $—(CH_2)_3—$, $—CH_2CH(CH_3)—$ oder $—CH_2C(CH_3)_2—$ bedeutet;

R ausgewählt ist aus (a) einer Phenylgruppe gegebenenfalls substituiert durch einen oder zwei Substituenten, je ausgewählt aus Nitro, Halo, $C_1—C_4$-Alkyl, $C_1—C_4$-Alkoxy, Hydroxy, Trifluormethyl und Cyano, (b) einer 1- oder 2-Naphthylgruppe und (c) Benzofuranyl; Benzothienyl; Pyridyl gegebenenfalls monosubstituiert mit Methyl oder Cyano; Chinolyl; Benzoxazolyl; Benzothiazolyl; Furyl; Pyrimidinyl; Thiazolyl; 2,1,3-Benzoxadiazol-4-yl; 2,1,3-Benzothiadiazol-4-yl; oder Thienyl gegebenenfalls mon - substituiert mit Halo oder $C_1—C_4$-Alkyl;

R^1 und R^2 je unabhängig $C_1—C_4$-Alkyl oder 2-Methoxyäthyl bedeuten; und

R^3 Wasserstoff, $C_1—C_4$-Alkyl, 2-($C_1—C_4$-Alkoxy)äthyl, Cyclopropylmethyl, Benzyl oder $—(CH_2)_mCOR^4$ bedeutet, worin m 1, 2 oder 3 und R^4 Hydroxy, $C_1—C_4$-Alkoxy oder $—NR^5R^6$ bedeutet, worin R^5 und R^6 je unabhängig Wasserstoff oder $C_1—C_4$-Alkyl bedeuten.

2. Verbindung nach Anspruch 1, worin R Phenyl, 2-Chlorphenyl, 2-Fluorphenyl 2-Methoxyphenyl, 3-Chlorphenyl, 2-Chlor-3-hydroxyphenyl, 2-Chlor-6-fluorphenyl oder 2,3-Dichlorphenyl ist.

3. Verbindung nach einem der vorhergehenden Ansprüche, worin Y $—(CH_2)_2—$ oder $—CH_2CH(CH_3)—$ ist.

4. Verbindung nach einem der vorhergehenden Ansprüche, worin R^3 H, CH_3, Benzyl, 2-Methoxyäthyl, $—CH_2COOCH_3$, $—CH_2COOC_2H_5$, $—CH_2CONH_2$, $—CH_2CONHCH_3$ oder $—CH_2COOH$ ist.

5. Verbindung nach Anspruch 4, worin R^3 H oder CH_3 ist.

6. Verbindung nach Anspruch 1, worin R 2-Chlorphenyl, R^1 CH_3, R^2 C_2H_5, Y $—(CH_2)_2—$ und R^3 H od r CH_3 sind.

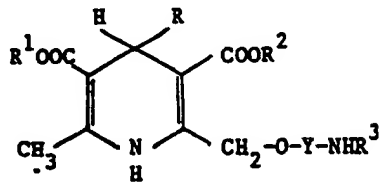
7. Verbindung nach einem der vorhergehenden Ansprüche in Form des Maleatsalzes.

8. Pharmazeutisches Präparat enthaltend eine Verbindung der Formel (I) oder ein pharmazeutisch verwendbares Säureadditionssalz davon mit einem pharmazeutisch verwendbaren Verdünnungsmittel oder Trägermaterial.

9. Verbindung der Formel (I) oder ein pharmazeutisch verwendbares Säureadditionssalz davon nach irgendeinem der Ansprüche 1 bis 7 zur Verwendung bei der Behandlung ischämischer Herzkrankheit, insbesondere Angina oder Hypert ni , beim Menschen.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung eines 1,4-Dihydropyridins der Formel



(I)

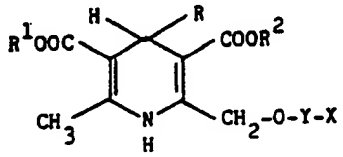
oder eines pharmazeutisch verwendbaren Säureadditionssalzes davon worin

Y $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2CH(CH_3)-$ oder $-CH_2C(CH_3)_2-$ bedeutet;

R ausgewählt ist aus (a) einer Phenylgruppe gegebenenfalls substituiert durch einen oder zwei Substituenten, je ausgewählt aus Nitro, Halo, C_1-C_4-Alkyl, C_1-C_4-Alkoxy, Hydroxy, Trifluormethyl und Cyano, (b) einer 1- oder 2-Naphthylgruppe und (c) Benzofuranyl; Benzothienyl; Pyridyl gegebenenfalls monosubstituiert mit Methyl oder Cyano; Chinolyl; Benzoxazolyl; Benzothiazolyl; Furyl; Pyrimidinyl; Thiazolyl; 2,1,3-Benzoxadiazol-4-yl; 2,1,3-Benzothiadiazol-4-yl; oder Thienyl gegebenenfalls monosubstituiert mit Halo oder C_1-C_4-Alkyl;

R^1 und R^2 je unabhängig C_1-C_4-Alkyl oder 2-Methoxyäthyl bedeuten; und

R^3 Wasserstoff, C_1-C_4-Alkyl, 2-(C_1-C_4-Alkoxy)äthyl, Cyclopropylmethyl, Benzyl oder $-(CH_2)_mCOR^4$ bedeutet, worin m 1, 2 oder 3 und R^4 Hydroxy, C_1-C_4-Alkoxy oder $-NR^5R^6$ bedeutet, worin R^5 und R^6 je unabhängig Wasserstoff oder C_1-C_4-Alkyl bedeuten, gekennzeichnet durch die Entfernung der Aminoschutzgruppe von einem Amino-geschützten 1,4-Dihydropyridin der Formel:



(IA)

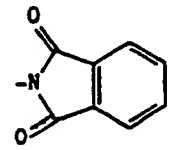
worin R, R^1, R^2 und Y die obige Bedeutung haben und X eine passende geschützte primäre oder sekundäre Aminogruppe ist, wobei diese sekundäre Aminogruppe die Formel $-NHR^3$ aufeist, worin R^3 die für Formel (I) angegebene Bedeutung mit Ausnahme von Wasserstoff hat, wobei dieses Verfahren gegebenenfalls von einem oder mehreren der folgenden Stufen gefolgt wird:

(a) Umwandlung einer Verbindung der Formel (I), in der R^3 H ist, in eine Verbindung der Formel (I), in der R^3 $-(CH_2)_mCOO(C_1-C_4$-Alkyl) ist, worin m 1, 2 oder 3 ist, durch Reaktion mit einer Verbindung der Formel Hal-$(CH_2)_mCOO(C_1-C_4$-Alkyl), worin "Hal" Cl oder Br ist;

(b) Umwandlung einer Verbindung der Formel (I), in der R^3 $-(CH_2)_mCOO(C_1-C_4$-Alkyl) ist, worin m 1, 2 oder 3 ist, in eine Verbindung der Formel (I), in der R^3 $-(CH_2)_mCOOH$ oder $-(CH_2)_mCONR^5R^6$ ist, worin m, R^5 und R^6 die für Formel (I) angegebene Bedeutung haben, durch Hydrolyse bzw. Reaktion mit einem Amin oder Formel R^5R^6NH; und

(c) Umwandlung einer Verbindung der Formel (I) in ein pharmazeutisch verwendbares Säureadditionssalz durch Reaktion mit einer nichttoxischen Säure.

2. Verfahren nach Anspruch 1, worin X $-NR^3$(benzyl), wobei R^3 die für Formel (I) angegebene Bedeutung hat, oder $-NR^3(COOCH_2CCl_3)$, wobei R^3 C_1-C_4-Alkyl ist, oder eine Gruppe der Formel



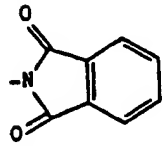
bedeutet.

3. Verfahren nach Anspruch 2, worin X $-NR^3$(benzyl) ist, wobei diese Benzylgruppe durch Behandeln der Verbindung der Formel (IA) mit Wasserstoff entfernt wird.

4. Verfahren nach Anspruch 3, w lches in Anwesenh it eines Palladiumkatalysators unter saur n Bedingungen durchgeführt wird.

5. Verfahren nach Anspruch 2, worin $-NR^3(COOCH_2CCl_3)$ ist und di se $-COOCH_2CCl_3$-Gruppe durch Behandlung der Verbindung der Formel (IA) mit Zink in Ameisen- oder Essigsäure entfernt wird.

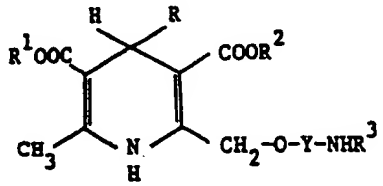
6. V rfahren nach Anspruch 1, w rin X eine Gruppe der Formel



ist, wobei die Phthaloylgruppe durch Behandlung von Verbindung (IA) mit entweder (a) einem primären Amin, (b) Hydrazinhydrat oder (c) einem Alkalimetallhydroxyd und dann mit Chlorwasserstoff oder Schwefelsäure entfernt wird.

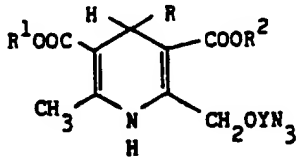
7. Verfahren nach Anspruch 6, worin dieses primäre Amin Methylamin ist und dieses Alkalimetallhydroxyd Kaliumhydroxyd ist.

8. Verfahren zur Herstellung eines 1,4-Dihydropyridins der Formel:



(I)

oder einem pharmazeutisch verwendbaren Säureadditionssalz davon,
worin
Y $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2CH(CH_3)-$ oder $-CH_2C(CH_3)_2-$ ist;
R die in Anspruch 1 angegebene Bedeutung hat;
R^1 und R^2 je unabhängig C_1-C_4-Alkyl oder 2-Methoxyäthyl sind; und
R^3 H oder $-(CH_2)_mCOR^4$ ist, wobei m 1, 2 oder 3 ist und
R^4 Hydroxy, C_1-C_4-Alkoxy oder $-NR^5R^6$ ist, wobei R^5 und R^6 je unabhängig Wasserstoff oder C_1-C_4-Alkyl sind, charakterisiert durch Reduktion einer Azidoverbindung der Formel:



worin R, R^1, R^2 und Y die für Formel (I) angegebene Bedeutung haben, unter Bildung einer Verbindung der Formel (I), in der R^3 Wasserstoff ist, wobei dieses Verfahren gegebenfalls von einer oder mehreren der folgenden Stufen gefolgt wird:

(a) Umwandlung einer Verbindung der Formel (I), in der R^3 H ist, in eine Verbindung der Formel (I), in der R^3 $-(CH_2)_mCOO(C_1-C_4$-Alkyl) ist, worin m 1, 2 oder 3 ist, durch Reaktion mit einer Verbindung der Formel Hal-$(CH_2)_mCOO(C_1-C_4$-Alkyl), worin "Hal" Cl oder Br ist;

(b) Umwandlung einer Verbindung der Formel (I), in der R^3 $-(CH_2)_mCOO(C_1-C_4$-Alkyl) ist, worin m 1, 2 oder 3 ist, in eine Verbindung der Formel (I), worin R^3 $-(CH_2)_mCOOH$ oder $-(CH_2)_mCONR^5R^6$ ist, wobei m, R^5 und R^6 die für Formel (I) angegebene Bedeutung haben, durch Hydrolyse bzw. Reaktion mit einem Amin der Formel R^5R^6; und

(c) Umwandlung einer Verbindung der Formel (I) in ein pharmazeutisch verwendbares Säureadditionssalz durch Reaktion mit einer nichttoxischen Säure.

9. Verfahren nach Anspruch 8, worin die Reduktion mit Wasserstoff durchgeführt wird.

10. Verfahren nach Anspruch 9, worin die Hydrierung in Anwesenheit eines Palladiumkatalysators durchgeführt wird.

11. Verfahren nach Anspruch 8, worin die Reduktion mit Zink und Salzsäure durchgeführt wird.

12. Verfahren nach einem der Ansprüche 1 bis 7, dadurch gekennzeichnet, dass es zur Herstellung von Verbindungen der Formel (I) verwendet wird, in der R 2-Chlorphenyl, R^1 CH_3, R^2 C_2H_5, Y $-(CH_2)_2-$ und R^3 H oder CH_3 sind.

13. Verfahren nach einem der Ansprüche 8 bis 11, dadurch gek nnzeichnet, dass es zur Herstellung von V rbindung der Form l (I) verw ndet wird, in der R 2-Chlorphenyl, R^1 CH_3, R^2 C_2H_5, Y $-(CH_2)_2$ und R^3 H sind.

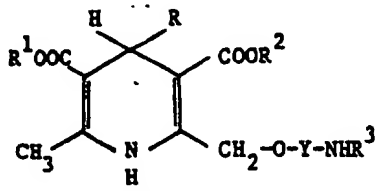
14. Verfahren zur Herstellung von pharmazeutischen Präparaten, welches darin besteht, dass man eine Verbindung der Formel (I) gemäss Definition in Anspruch 1 oder ein pharmaz utisch verwendbares Säureadditi nssalz davon durch ein Verfahren gemäss ein m der vorhergehenden Ansprüche herstellt, gefolgt

v m Mischen des so hergestellten Produktes mit einem pharmazeutisch verw ndbaren Verdünnungsmittel oder Trägermaterial.

15. Verfahren zur Herstellung eines pharmazeutischen Präparates, welches darin besteht, dass man eine Verbindung der Formel (I) gemäss Definition in Anspruch 1 oder ein pharmazeutisch verwendbares Säureadditionssalz davon mit einem pharmazeutisch verwendbaren Verdünnungsmittel oder Trägermaterial vermischt.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Dihydropyridine de formule:



(I)

ou un sel d'addition d'acide pharmaceutiquement acceptable correspondant

formule dans laquelle

Y représente $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2CH(CH_3)-$ ou $-CH_2C(CH_3)_2-$;

R est choisi entre (a) un groupe phényle éventuellement substitué par un ou deux substituants choisis chacun entre des substituants nitro, halogéno, alkyle en C_1 à C_4, alkoxy en C_1 à C_4, hydroxy, trifluorométhyle et cyano, (b) un groupe 1- ou 2-naphtyle et (c) un groupe benzofurannyle; benzothiényle; pyridyle éventuellement monosubstitué par un radical méthyle ou cyano; quinolyle; benzoxazolyle; benzothiazolyle; furyle; pyrimidinyle; thiazolyle; 2,1,3-benzoxadiazole-4-yle; 2,1,3-benzothiadiazole-4-yle; ou thiényle éventuellement monosubstitué par un radical halogéno ou alkyle en C_1 à C_4;

R^1 et R^2 représentent chacun, indépendamment un groupe alkyle en C_1 à C_4 ou 2-méthoxyéthyle; et

R^3 est l'hydrogène, un groupe alkyle en C_1 à C_4, 2-(alkoxy en C_1 à C_4)éthyle, cyclopropylméthyle, benzyle ou $-(CH_2)_mCOR^4$ ou m a la valeur 1, 2 ou 3 et R^4 est un groupe hydroxy, alkoxy en C_1 à C_4 ou $-NR^5R^6$, R^5 et R^6 représentant chacun, indépendamment, l'hydrogène ou un groupe alkyle en C_1 à C_4.

2. Composé suivant la revendication 1, dans lequel R est un groupe phényle, 2-chlorophényle, 2-fluorophényle, 2-méthoxyphényle, 3-chlorophényle, 2-chloro-3-hydroxyphényle, 2-chloro-6-fluorophényle ou 2,3-dichlorophényle.

3. Composé suivant l'une ou l'autre des revendications précédentes, dans lequel Y est un groupe $-(CH_2)_2-$ ou $-CH_2CH(CH_3)-$.

4. Composé suivant l'une quelconque des revendications précédentes, dans lequel R^3 représente H, un groupe CH_3, benzyle, 2-méthoxyéthyle, $-CH_2COOCH_3$, $-CH_2COOC_2H_5$, $-CH_2CONH_2$, $-CH_2CONHCH_3$ ou $-CH_2COOH$.

5. Composé suivant la revendication 4, dans lequel R^3 représente H ou un groupe CH_3.

6. Composé suivant la revendication 1, dans lequel R est un groupe 2-chlorophényle, R^1 est un groupe CH_3, R^2 est un groupe C_2H_5, Y est un groupe $-(CH_2)_2-$ et R^3 représente H ou CH_3.

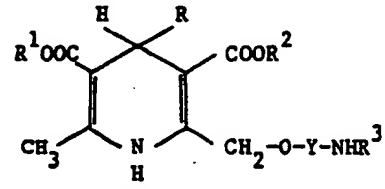
7. Composé suivant l'une quelconque des revendications précédentes, qui est sous la forme d'un sel d'acide maléique.

8. Composition pharmaceutique comprenant un composé de formule (I) ou un sel d'addition d'acide pharmaceutiquement acceptable de ce composé en association avec un diluant ou support acceptable du point de vue pharmaceutique.

9. Composé de formule (I) ou un sel d'addition d'acide pharmaceutiquement acceptable de ce composé suivant l'une quelconque des revendications 1 à 7, destiné à être utilisé dans le traitement d'une maladie cardiaque ischémique en particulier de l'angine, ou de l'hypertension, chez un être humain.

Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'une 1,4-dihydropyridine de formule:



(I)

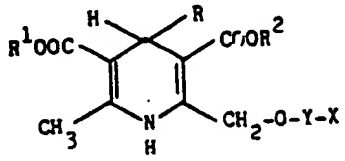
u d'un sel d'addition d'acide pharmaceutiqu ment acc ptable de c c mposé, formula dans laquell

Y représente $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2CH(CH_3)-$ ou $-CH_2C(CH_3)_2-$;

R est choisi entr (a) un groupe phényle éventuellement substitué par un ou deux substituants choisis chacun entre des substituantes nitro, halogéno, alkyle n C_1 à C_4, alkoxy en C_1 à C_4, hydroxy, triflu ro-méthyle et cyano, (b) un groupe 1- u 2-naphtyle et (c) un gr upe benzofurannyle; benzothiényle; pyridyle éventuellement monosubstitué par un radical méthyle u cyano; quinolyle; benzoxazolyle; b nz - thiazolyle; furyle; pyrimidinyle; thiazolyle; 2,1,3-benzoxadiazole-4-yle; 2,1,3-benzothiadiazole-4-yle; ou thiényle éventuellement monosubstitué par un radical halogéno ou alkyle en C_1 à C_4;

R^1 et R^2 représentent chacun, indépendamment un groupe alkyle en C_1 à C_4 ou 2-méthoxyéthyle; et

R^3 est l'hydrogène, un groupe alkyle en C_1 à C_4, 2-(alkoxy en C_1 à C_4)éthyle, cyclopropylméthyle, benzyle ou $-(CH_2)_mCOR^4$ ou m a la valeur 1, 2 ou 3 et R^4 est un groupe hydroxy, alkoxy en C_1 à C_4 ou $-NR^5R^6$, R^5 et R^6 représentant chacun, indépendamment, l'hydrogène ou un groupe alkyle en C_1 à C_4, caractérisé par l'élimination du groupe protégeant la fonction amino d'une 1,4-dihydropyridine à fonction amino protégée de formule:



(IA)

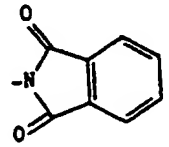
dans laquelle R, R^1, R^2 et Y sont tels que définis ci-dessus et X représente, selon le cas, un groupe amino primaire ou secondaire protégé, le groupe amino secondaire ayant la formule $-NHR^3$ dans laquelle R^3 est tel que défini pour la formule (I), excepté l'hydrogène, ledit procédé étant suivi, le cas échéant, d'une ou plusieurs des étapes suivantes:

(a) transformation d'un composé de formule (I) dans laquelle R^3 représente H en un composé de formule (I) dans laquelle R^3 représente $-(CH_2)_mCOO$(alkyle en C_1 à C_4) où *m* a la valeur 1, 2 ou 3 par réaction avec un composé de formule Hal-$(CH_2)_m$COO(alkyle en C_1 à C_4) où "Hal" est Cl ou Br;

(b) transformation d'un composé de formule (I) dans laquelle R^3 représente un groupe $-(CH_2)_mCOO$(alkyle en C_1 à C_4) dans lequel *m* a la valeur 1, 2 ou 3, en un composé de formule (I) dans laquelle R^3 est un groupe $-(CH_2)_mCOOH$ ou $-(CH_2)_mCONR^5R^6$, *m*, R^5 et R^6 ayant les définitions données pour la formule (I), respectivement par hydrolyse ou par réaction avec une amine de formule R^5R^6NH; et

(c) transformation d'un composé de formule (I) en un sel d'addition d'acide pharmaceutiquement acceptable par réaction avec un acide non toxique.

2. Procédé suivant la revendication 1, dans lequel X est un groupe $-NR^3$ (benzyle) dans lequel R^3 a la définition donnée pour la formule (I), un groupe de formule $-NR^3(COOCH_2CCl_3)$ dans laquelle R^3 est un radical alkyle en C_1 à C_4, ou un groupe de formule:

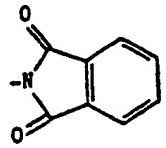


3. Procédé suivant la revendication 2, dans lequel X est un groupe $-NR^3$(benzyle), ledit groupe benzyle étant éliminé par traitement du composé (IA) avec l'hydrogène.

4. Procédé suivant la revendication 3, qui est mis en oeuvre en présence d'un catalyseur à base d palladium dans des conditions acides.

5. Procédé suivant la revendication 2, dans lequel X est un groupe $-NR^3(COOCH_2CCl_3)$ et ledit groupe $-COOCH_2CCl_3$ est éliminé par traitement du composé (IA) avec du zinc dans l'acide formique ou acétique.

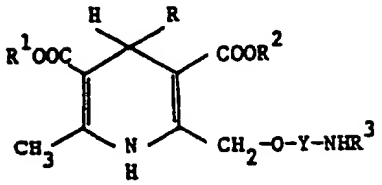
6. Procédé suivant la revendication 1, dans lequel X est un groupe de formule:



le groupe phtaloyle étant éliminé par traitement du composé (IA) av c (a) un amine primaire, (b) l'hydrate d'hydrazine ou (c) un hydroxyde d métal alcalin, puis av c l'acide chl rhydrique ou sulfurique.

7. Procédé suivant la revendication 6, dans lequel l'amine primaire est la méthyleamine et l'hydr xyde de métal alcalin est l'hydroxyde de potassium.

8. Pr cédé de préparation d'un 1,4-dihydr pyridine de formule:



(I)

ou d'un sel d'addition d'acide pharmaceutiquement acceptable de ce composé, formule dans laquelle

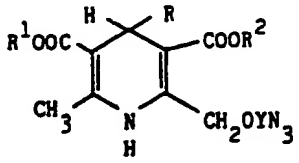
Y est un groupe $—(CH_2)_2—$, $—(CH_2)_3—$, $—CH_2CH(CH_3)—$ ou $—CH_2C(CH_3)_2—$;

R a la définition donnée dans la revendication 1;

R^1 et R^2 représentent chacun, indépendamment, un groupe alkyle en C_1 à C_4 ou le groupe 2-méthoxyéthyle; et

R^3 représente H ou un groupe $—(CH_2)_mCOR^4$ dans lequel *m* a la valeur 1, 2 ou 3 et

R^4 est un groupe hydroxy, alkoxy en C_1 à C_4 ou $—NR^5R^6$ où R^5 et R^6 représentent chacun, indépendamment, l'hydrogène ou un groupe alkyle en C_1 à C_4, caractérisé par la réduction d'un composé azido de formule:



dans laquelle R, R^1, R^2 et Y sont tels que définis pour la formule (I) de manière à produire un composé de formule (I) dans laquelle R^3 représente H, ledit procédé étant suivi, le cas échéant, d'une ou plusieurs des opérations suivantes:

(a) transformation d'un composé de formule (I) dans laquelle R^3 représente H en un composé de formule (I) dans laquelle R^3 représente un groupe $—(CH_2)_mCOO$(alkyle en C_1 à C_4) où *m* a la valeur 1, 2 ou 3, par réaction avec un composé de formule Hal-$(CH_2)_mCOO$(alkyle en C_1 à C_4) où "Hal" représente Cl ou Br,

(b) transformation d'un composé de formule (I) dans laquelle R^3 est un groupe $—(CH_2)_mCOO$(alkyle en C_1 à C_4) dans laquelle *m* a la valeur 1, 2 ou 3 en un composé de formule (I) dans laquelle R^3 est un groupe $—(CH_2)_mCOOH$ ou $—(CH_2)_mCONR^5R^6$, *m*, R^5 et R^6 étant tels que définis pour la formule (I), respectivement par hydrolyse ou par réaction avec une amine de formule R^5R^6NH; et

(c) transformation d'un composé de formule (I) en un sel d'addition d'acide pharmaceutiquement acceptable par réaction avec un acide non toxique.

9. Procédé suivant la revendication 8, dans laquel la réduction est effectuée avec de l'hydrogène.

10. Procédé suivant la revendication 9, dans lequel l'hydrogénation est conduite en présence d'un catalyseur au palladium.

11. Procédé suivant la revendication 8, dans lequel la réduction est effectuée avec du zinc et de l'acide chlorhydrique.

12. Procédé suivant l'une quelconque des revendications 1 à 7, caractérisé en ce qu'il est utilisé pour préparer des composés de formule (I) dans laquelle R est le groupe 2-chlorophényle, R^1 est le groupe CH_3, R^2 est le groupe C_2H_5, Y est le groupe $—(CH_2)_2—$ et R^3 représente H ou CH_3.

13. Procédé suivant l'une quelconque des revendications 8 à 11, caractérisé en ce qu'il est utilisé pour préparer des composés de formule (I) dans laquelle R est le groupe 2-chlorophényle, R^1 est le groupe CH_3, R^2 est le groupe C_2H_5, Y est le groupe $—(CH_2)_2—$ et R^3 représente H.

14. Procédé de préparation d'une composition pharmaceutique, qui consiste à préparer un composé de formule (I) tel que défini dans la revendication 1 ou un sel d'addition d'acide pharmaceutiquement acceptable de ce composé par un procédé suivant l'une quelconque des revendications précédentes, suivi du mélange du produit ainsi formé avec un diluant ou support pharmaceutiquement acceptable.

15. Procédé de préparation d'une composition pharmaceutique, qui consiste à mélanger un composé de formule (I) tel que défini dans la revendication 1 ou un sel d'addition d'acide pharmaceutiquement acceptable de ce composé avec un diluant ou support acceptable du point de vue pharmaceutique.